From Department of Medical Epidemiology and Biostatistics
Karolinska Institutet, Stockholm, Sweden

STRESS DURING CANCER DIAGNOSTIC WORKUP

Qing Shen

Karolinska Institutet

Stockholm 2020

Front cover illustration by 橙梓
Published by Karolinska Institutet
Printed by Eprint AB 2020

ISBN 978-91-7831-720-2

Stress During Cancer Diagnostic Workup

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Qing Shen

April 17th, 2020. 09:00 a.m.
Lecture hall Atrium, Nobels väg 12B, Karolinska Institutet, Solna

Principal Supervisor:
Professor Fang Fang
Karolinska Institutet
Institute of Environmental Medicine
Unit of Integrative Epidemiology

Co-supervisor(s):
Associate Professor Maria E C Schelin
Lund University
Institute for Palliative Care
Department of Clinical Science

Associate Professor Yang Cao
Örebro University
Clinical Epidemiology and Biostatistics
School of Medical Sciences

Professor Pär Sparén
Karolinska Institutet
Department of Medical Epidemiology and Biostatistics

Opponent:
Professor Ping Qin
University of Oslo
National Centre for Suicide Research and Prevention

Examination Board:
Professor Yvonne Brandberg
Karolinska Institutet
Department of Oncology-Pathology

Associate Professor Sarah Bergen
Karolinska Institutet
Department of Medical Epidemiology and Biostatistics

Associate Professor Marija Cvijovic
University of Gothenburg
Department of Mathematical Sciences
Applied Mathematics and Statistics

To all in the fight against diseases

ABSTRACT

Receiving a cancer diagnosis is an extremely stressful life event. Cancer patients have been reported to experience an excessive risk of stress-related health outcomes including suicide. The time period between the first suspicion of a potential cancer and cancer diagnosis or start of primary cancer treatment is commonly defined as “cancer diagnostic workup”. This critical time window is especially stressful, mainly due to the uncertainty about the final diagnosis. Such diagnostic process and its health consequences may also apply to a larger group of population who are evaluated for but never receive a cancer diagnosis. Till now, less attention has been devoted to the health impact of a cancer diagnostic workup. This thesis aims to assess the risk of different stress-related health outcomes during a cancer diagnostic workup, taken into account various diagnostic processes, individuals with or without a final diagnosis of cancer, and different reasons of workup initiation. We also investiagated effect of a potential treatment in modulating the excessive risk of stress-related health outcomes following a cancer diagnosis.

In study I, we examined the risk of iatrogenic and non-iatrogenic injuries during weeks before and after diagnosis among all patients with cancer. To eliminate impact of shared risk factors between cancer and injuries, we compared the risk from 16 weeks before to 16 weeks after cancer diagnosis, to the same period one year earlier, of the same patient. We found that cancer patients had an increased rate of both iatrogenic and non-iatrogenic injuries requiring inpatient care shortly before and after cancer diagnosis, compared to one year before. Our findings shed further light on the total burden of medical complications and call for prevention of intentional and unintentional injuries during the diagnostic process of a cancer.

In study II, we assessed the risk of injuries that required inpatient care in relation to the diagnostic workup of cervical cancer and its precursor lesions, among all women that participated screening for cervical cancer. Women diagnosed with invasive cervical cancer and its precursors lesions were identified from the National Cervical Screening Register as exposed to a diagnostic workup. Women who had a normal result in Pap smear were classified as referece group. Inpatient care of either iatrogenic injuries or non-iatrogenic injuries was extremely rare during the diagnostic procedures of cervical cancer and its precursor lesions. Although with a small number of outcomes, we still found that women with invasive cervical cancer had an increased rate of non-iatrogenic injuries in relation to receiving a diagnosis of cervical cancer.

In study III, we investigated the risk of psychiatric disorders and cardiovascular diseases during the diagnostic workup of potential breast cancer. All women diagnosed with a breast cancer, a benign tumor in breast, or unspecified lump in breast, were identified and considered as exposed to a diagnostic workup of potential breast cancer. We compared the risks of psychiatric disorders and cardiovascular diseases during the six weeks before diagnosis of the exposed women to the risks among the unexposed women. We found that women with benign tumor and breast cancer had an increased rate of psychiatric disorders and cardiovascular diseases while waiting for the final diagnosis.

In study IV, we aimed to assess the use of low-dose aspirin and non-aspirin NSAIDs in relation to the risk of unnatural death due to suicide or accidents among patients after receiving a cancer diagnosis. Cancer patients with aspirin or non-aspirin NSAIDs dispensed after diagnosis were considered to be medicated. We compared the risk of unnatural death during on-medication period with the risk during off-medication period. We found that aspirin intake was associated with a lower risk of unnatural death after a cancer diagnosis. We did however not find a statistically significant association between use of non-aspirin NSAIDs and risk of unnatural death.

In conclusion, a cancer diagnostic workup is associated with increased risks of a spectrum of stress-related health outcomes. Such increased risks of health outcomes, including injuries, psychiatric disorders and cardiovascular diseases, are noted for a large group of individuals being evaluated for a potential cancer, regardless of the final diagnosis. It represents therefore a great disease burden for the society. Interventions, such as low-dose aspirin intake, might be effective in reducing such risks (e.g. risk of unnatural death), after cancer diagnosis.

LIST OF SCIENTIFIC PAPERS

*Equal contribution.

I. **Shen Q***, Lu D*, Schelin MEC, Jöud A, Cao Y, Adami HO, Cnattingius S, Fall K, Valdimarsdóttir U, Fang F. Injuries before and after diagnosis of cancer: nationwide register based study. BMJ. 2016; 354:i4218

II. **Shen Q**, Lu D, Andrae B, Schelin MEC, Sjölander A, Cao Y, Sparén P, Fang F. Injuries in relation to the diagnostic procedures of cervical cancer and its precursor lesions: a nationwide cohort study in Sweden. Manuscript submitted.

III. **Shen Q**, Jöud A, Schelin MEC, Sjölander A, Cao Y, Sparén P, Fall K, Czene K, Valdimarsdóttir U, Fang F. Psychiatric disorders and cardiovascular diseases during the diagnostic workup of potential breast cancer: a population-based cohort study in Skåne, Sweden. Breast Cancer Research. 2019; 21:139

IV. **Shen Q**, Sjölander A, Sloan E, Walker A, Fall K, Valdimarsdóttir U, Smedby KE, Fang F. NSAID use and unnatural deaths after cancer diagnosis: a nationwide cohort study in Sweden. Manuscript.

CONTENTS

LIST OF ABBREVIATIONS

CI	Confidence Interval
IR	Incidence rate
IRR	Incidence rate ratio
HR	Hazard Ratio
NKCx	Swedish National Cervical Screening Registry
CIN	Cervical intraepithelial neoplasia
SNS	Sympathetic nervous system
HPA	Hypothalamic-pituitary-adrenal axis
SHR	Skåne Healthcare Register
HPV	Human papillomavirus
Pap smear	Papanicolaou smear
MRI	Magnetic resonance imaging
NSAID	Nonsteroidal anti-inflammaotry drug
COX	Cyclooxygenase
ATC	Anatomical Therapeutic Chemical
LISA	The Longitudinal Integration Database for Health Insurance and Labor Market Studies
SCB	Statistics Sweden
PIN	The personal identification number
ICD	International Classification of Disease
LSIL	Low grade lesion
HSIL	High grade lesion
AIS	Adenocarcinoma *in situ*
PAF	Population attributable fraction

1 INTRODUCTION

Stress and stress response to cope with changes in surroundings are common in daily life. Normal stress response is triggered by a stressor, a stimulus that can disrupt or threaten homeostatic balance, and is positive in most cases to adapt to changed situation, known as "eustress". When stressors become excessive to adapt to, they can be harmful and affect psychical and mental conditions (termed as "distress"), resulting in stress-related health outcomes. Common signs of stress overload include, although not limit to, anxiousness, fatigue, insomnia, headache, poor concentration, negative thoughts, social isolation, etc.

Receiving a cancer diagnosis is, among others, an extremely stressful life event. Compared with other patients, cancer patients have a higher burden of morbidity and mortality (1), largely attributed to the complex pathophysiology of the underlying malignant disease, the side effects of different cancer treatments, or simply the burden of having a progressing and fatal disease. Recently, cancer patients have been recognized to experience a wide spectrum of stress-related health outcomes, ranging from depression, anxiety, to severe outcomes such as acute cardiovascular events and suicide (2). Although the number of patients living with a cancer is increasing worldwide (3), the experience and its impact of psychological stress on patients with a cancer has not been fully investigated.

Psychological stress can be measured directly by level of stress hormones in bio-samples, self-reported measurements on stress symptoms, or questionnaires assessing stress experience and stress resilience (4). Besides, psychological stress can also be evaluated by assessing stress-related health outcomes, as proxies to quantify its impact on patients who perceive a stressor. A comprehensive assessment of stress-related health outcomes among cancer patients from clinical evaluation to diagnosis and treatment has rarely been performed. Further, whether a potential intervention can attenuate the excessive risk of stress-related health outcomes in relation to cancer, is of great clinical importance.

Therefore, the purpose of this thesis is to enhance the understanding of the impact from psychological stress on various stress-related health outcomes among patients being evaluated for a cancer, and to explore the potential effect of anti-inflammatory treatment in reducing such health outcomes, by taking the most advantage of the large population and health registers in Sweden. Findings obtained from this thesis may assist the healthcare providers, the families, and the society at large, in providing proper support, not only after cancer diagnosis but also during the clinical evaluation of a potential cancer.

2 BACKGROUND

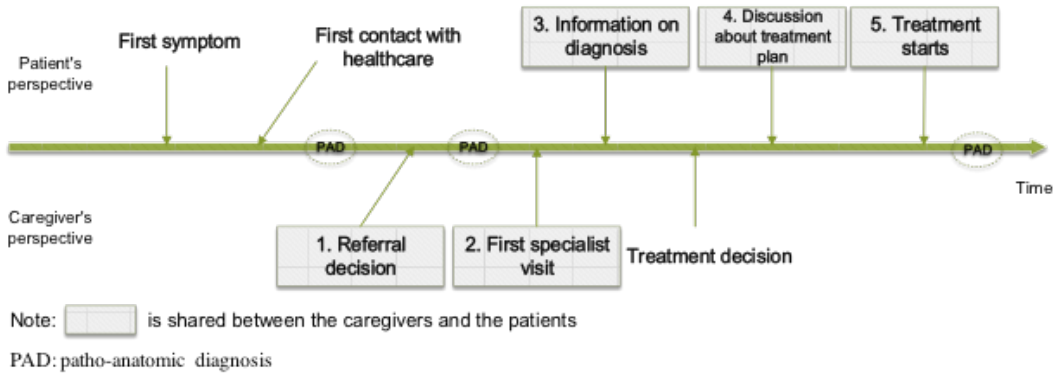
2.1 PSYCHOLOGICAL STRESS AND CANCER DIAGNOSIS

2.1.1 Cancer diagnosis - a stressful life event

The detection and treatment of cancer at early stage of disease progression improves short- and long-term survival. For many cancers, the prognosis and survival of patients with small size and localized tumor is generally better than those with advanced or metastatic tumor (5). Apart from the late onset of cancer symptoms, delay in referral to disease evaluation, diagnosis and treatment, can as well have considerable adverse health impact. It has been noted that longer delay in time between onset of symptoms and start of treatment was associated with advanced tumor stage and higher morbidity and mortality (6–8), although some found the association to be less clear or null (9,10). A recent systematic review found an evident association between shorter waiting time to diagnosis and better clinical outcomes in patients with cancers of breast, colorectal, head and neck, testicular and melanoma (11).

In order to improve the variations in cancer survival and other comorbidities attributed to the delay in referral in cancer care, many countries start to establish comprehensive national cancer guidelines (12–15). In Denmark, a better survival and reduced mortality was reported among symptomatic cancer patients after the implementation of the Danish *Cancer Patient Pathways* (16). In Sweden, an investigation of national cancer strategy stated a lack of comprehensive review of waiting time in cancer care and a dissatisfaction among patients regarding organization and information delivery (17). To measure waiting time in cancer care, a model was established to cover the initial parts of the care path from referral decision to treatment start, with focus on patients' perspective (Figure 2.1).

Figure 2.1 Cancer pathway through care – model for measuring waiting time in Sweden, translated from report *Vänterider i cancervården* from the Swedish National Board of Health and Welfare (18).



Based on this model, the Swedish National Board of Health and Welfare conducted a measurement of waiting time in cancer care, from referral decision until the start of treatment, for the most common cancer types (18). In this report, there was a discrepancy in the waiting time according to cancer characteristics as well as across regions. Patients diagnosed with advanced tumor stage had shorter waiting time than other patients, indicating that these patients were prioritized in the care system. The median waiting time was up to one month from

referral-to-specialist to treatment for all forms of cancer, except for prostate cancer. For patients with kidney cancer, rectal cancer and head and neck cancer, the median waiting time was close to two months (Table 2.1).

Table 2.1 Waiting time from referral decision until the start of treatment for the most common cancer types in Sweden, report from the Swedish National Board of Health and Welfare, 2015 (19).

Cancer type	Median waiting time in days (1st – 3rd quarters)
Breast cancer	20 (13-28)
Skin melanoma	37 (23-58)
Head and neck cancer	50 (35-70)
Lung cancer	30 (15-50)
Stomach cancer	20 (10-36)
Esophageal cancer	19 (11-35)
Kidney cancer	64 (42-104)
Prostate cancer	Remote metastatic: 43 (20-71) Intermediate and high-risk prostate cancer: 167 (125-223)
Colon cancer	42 (29-60)
Bladder cancer	36 (22-55)
Rectal cancer	56 (43-78)

Starting from 2015, to ensure equitable and accessible cancer care, the Swedish government has introduced standardized care pathways for different cancers. The purpose is to shorten unnecessary waiting time, reduce regional differences, provide better information, and to have more coherent care process and generally more satisfaction in cancer care for all patients (20).

2.1.2 Cancer diagnostic workup

Studies have predominantly investigated the health impact of waiting time to diagnosis and treatment on cancer survival (11). However, less attention is devoted to potential health risks during the time period from the first suspicion of cancer to start of treatment (commonly defined as "cancer diagnostic workup"). A cancer diagnostic workup usually starts when patients first contact with healthcare or participate in cancer screening, through referral decision, specialist visit, diagnosis, until the start of treatment (Figure 2.1). Primary treatment commonly includes surgery, radiotherapy, chemotherapy, and combined with other therapies (hormonal therapy, immune therapy, etc.), according to tumor characteristics and patients' conditions.

Evidence has nevertheless started to accumulate suggesting that the workup of a potential cancer, together with the treatment consequences, induces severe emotional turmoil that might result in significant health problems (21,22). The health impact of cancer diagnostic workup is not only pertinent to patients who are eventually diagnosed with cancer, but also to individuals who are evaluated for but do not have a cancer diagnosis. So far, knowledge about the precise population size of individuals who have been suspected for cancer but do not receive a cancer diagnosis is limited. In the United States, less than 20% of the children and teenagers who were evaluated for a potential cancer received eventually a cancer diagnosis and subsequent treatment, indicating that over 80% of the cancer workups were exploratory and did not result in a diagnosis of cancer (23). For adults, the proportions of verified cancer cases among primary

healthcare referrals for suspicious cancers appear to vary widely for different cancer types, from 3-11% for breast cancer (24), 25% for prostate cancer (25), and 60% for skin cancers (26,27). Moreover, the recent advancement in early cancer detection (e.g., via various screening activities) has the potential of introducing cases with false-positive test result and the subsequent over-treatment of cancer, which may further contribute to the extra burden in cancer care (28,29).

2.1.3 Health outcomes related to cancer diagnostic workup

2.1.3.1 Stress-related health outcomes

A diagnostic workup of cancer was found to clearly affect health and well-being, particularly psychosocial functioning. Affected domains might vary for different cancers, but generally include distress, fear and worry about having or getting a cancer, anxiety, mood changes, sense of uncertainty, disturbances in family, social and sexual roles, behavioral symptoms such as crying, sleep disturbance, and irritability, concerns about future reproduction (28,30,31). Researchers from the UK had extensively measured psychological distress along the diagnostic workup in men being evaluated for prostate cancer using questionnaires (21). More than half of patients scored waiting for biopsy result as the most stressful event, in contrast with only 4% that reported the procedure itself to be most stressful (21). To date, few studies have addressed the risks of concrete health outcomes related to psychological stress during a cancer diagnostic workup, although such impact is increasingly suggested (21,30,32).

Psychiatric disorders

Psychiatric disorders, in particular, depression, are commonly recognized health outcomes among cancer patients. In oncological settings, the prevalence of all types of depression is about 20% (33), and is significantly higher compared with a prevalence of 5-9% in general population (34,35). The prevalence of having any mood disorder is even higher, i.e., around 40% (33). It has been noted that children undergoing a diagnostic workup of cancer and their parents had an increased risk of anxiety and depression (23). In adults, an increased risk of hospitalization for depression was reported after a cancer diagnosis, mainly during the first year following a diagnosis (36). Such risk increase remained during the subsequent years for most cancer types (36). A recent study investigated the risk of any mental disorder among cancer patients, and demonstrated an increased risk of mental disorders starting from one year before cancer diagnosis onward (37). The risk elevation during the year before cancer diagnosis was speculated as a result of cancer symptoms and severe psychological distress experienced during clinical evaluation of a suspected cancer (33). However, few studies have assessed the risk of psychiatric disorders during the process of clinical evaluation for cancer.

Cardiovascular diseases

Evidence has accumulated suggesting the link between psychological stress and cardiovascular morbidity and mortality (34,35). Psychological distress experienced in daily life has been well established to be associated with the acute onset of cardiovascular diseases, such as myocardial

infarction and cardiac events (36,37). Higher risks of cardiovascular comorbidities have also been increasingly recognized among cancer patients (38). Cardiovascular conditions and hypertension are the most frequently identified comorbidities among cancer patients (39). More and more studies reported a higher rate of deaths from non-cancer causes among cancer patients than cancer causes, with cardiovascular disease as the leading cause of non-cancer mortality (1). The increase in risk of cardiovascular deaths was highest during the first weeks after cancer diagnosis and remained elevated, although with declining magnitude over time, during the first year after diagnosis (22,40,41). In addition to fatal outcomes, an increased risk of hospitalizations due to venous thromboembolism was reported among cancer patients, compared to the general population (42). The risk increase was more prominent for patients with metastatic tumors compared to other patients (41). The physical burden of a progressing disease, the cancer treatment, and the psychological distress induced by the cancer diagnosis, might collectively contribute to the risk increase. To date, evidence is still limited in understanding the risk of cardiovascular diseases before cancer diagnosis, especially when the patients are evaluated for a potential cancer.

Intentional injuries

Intentional self-inflicted injuries, such as suicide, are common among cancer patients (43). The prevalence of suicidal behaviors in general was estimated to be around 30% among patients with cancer (44,45). Cancer patients have around two times higher rate of suicide, compared to the general population (45). A large population-based cohort study found a 12-fold risk increase of suicide during the first week after cancer diagnosis, and the risk attenuated but remained increased during the first year after cancer diagnosis (22). Similar risk increase has thereafter been reported from many countries (46–48), both among young and adult cancer patients (40,41,49). Studies have provided evidence showing a greater risk increase of suicide among male and older patients, and patients with depression, advanced tumor stage or metastatic disease, as well as patients who were recently diagnosed with cancer (43,45,46). Although large proportion of cancer patients with suicidal ideation were reported to have major depression (50), the relative risk of suicide was higher among patients without such comorbidity (22). This is possibly be explained by the lower risk of suicide among individuals without depression. More studies are needed to explore the impact of cancer-related psychological stress on self-inflicted injuries, for instance, by focusing on non-fatal outcomes during clinical evaluation for a cancer.

Unintentional accidents

Besides deliberate self-harm, other external caused injuries or accidents, are common health outcomes among the elderly, representing a major health burden in old population. It was estimated that around 27% of the old adults fell at least once per year (51), among which, 10% might be severe injuries including fractures, joint dislocations and concussions (52). Despite being a common health outcome, such injuries are less investigated in cancer patients. Recently, a study from the UK investigated the association between hospital admissions and deaths due to self-harm and accidents within five years after cancer diagnosis, reporting an

increased risk of fatal and hospitalized accidents (53). The number of accidental outcomes was truly greater than suicide (53). An increased risk of death due to accidents was further identified during the first year after cancer diagnosis (47,54). Shared patient characteristics exist between suicide and accidental deaths, including physical, social and emotional dysfunctions (55). It was evident that depressive symptoms are risk factors for accidents such as falls and suicidal outcomes (56). Considering the absolute risk of the outcomes, the burden of accidents is of great public health importance and a potential threat to cancer patients' quality of life. However, evidence is scarce regarding the impact of a recent cancer diagnosis or cancer diagnostic workup on such injuries.

To conclude, being diagnosed with cancer stands for a fundamental challenge for cancer patients, both physically and psychologically. There is a great burden of different stress-related health outcomes among cancer patients (43). As the majority of attention is being paid to the later phase of the disease course, more knowledge is needed to better understand the health impact of cancer diagnostic workup, in addition to the eventual diagnosis, treatment and survivorship.

2.1.3.2 Other health outcome- Iatrogenic injuries

Cancer diagnostic workup is a period of time overwhelmed by a sequence of intensive medical examinations as well as subsequent treatment. Individuals evaluated for a potential cancer have more opportunities to be exposed to medical procedures and biological substances, and are more likely to suffer from iatrogenic injuries. Iatrogenic injuries can be defined as the unintended act from care process that might cause harm to the patients, and can also be referred to as medical complications, medical error or medical adverse events. Such injuries are estimated to be the third leading cause of death in the United States (57). However, the statistics of these injuries in general is limited.

Although systematic assessment in cancer patients is lacking, evidence has nevertheless suggested high burden of iatrogenic injuries among patients with severe illness. In a sample of randomly selected hospitals, the adverse events related to medical care were reported in 3.7% of hospitalized patients, including mostly temporally disabling injuries but also permanently disabling injuries (2.6%) and death (13.6%) (59). A medical record review study revealed that 16.6% of hospital admissions were associated with an adverse event resulting in disability or a longer hospital stay, of which, 13.7% were permanent disability and 4.9% were death (60). Human error was found to be the prominent cause (61). Wilson et al. reported that half of the medical adverse events occurred during surgery, and the others were diagnostic errors and drug complications (58,62). The rate of adverse events was higher among older, compared to younger, patients (59,63). Medical complications induced by human errors can be avoided, with 30-90% of adverse events estimated to be preventable (63–65). So far, the burden of iatrogenic injuries is not well identified among cancer patients, due to limited studies.

2.2 CERVICAL CANCER

Cervical cancer represents the fourth most common cancer in women, with approximately 570,000 cases and 311,000 deaths from cervical cancer in 2018 worldwide (66). The incidence of cervical cancer varies largely across countries. In Sweden, cervical cancer ranked as the 13th most common cancer in 2015, with a number of 563 new cancer cases and 163 deaths from this cancer (67). Great improvements have been achieved due to implementation of cervical screening. Nowadays, cervical cancer mostly affects women in less developed countries, where effective screening protocols are yet in place.

The most important risk factor and necessary cause of cervical cancer is the persistent infection with carcinogenic human papillomavirus (HPV) (68). HPV infection is common, with an estimated prevalence of about 11% in general population (69). Despite of the pivotal role of HPV infection on the formation and progression of cervical precursor lesions, most infection can be cleared and suppressed by human immune system within 1-2 years (70). About 10% of the infection can persist for years and are highly correlated with the development of cervical cancer and cancer precursors (70). Other risk factors, including smoking (71), hormonal contraception use (72), and risky sexual behaviors (73), may interact with HPV infection and contribute to carcinogenesis. It usually takes several years for cervical cancer to develop from precancerous lesions. The abnormal histological diagnoses include cervical intraepithelial neoplasia grade 1-3 (CIN 1-3), cervical adenocarcinoma *in situ*, and invasive squamous cervical cancer and invasive cervical adenocarcinoma. The precancerous lesions have the same potential to regress, to persistent, or to progress. A study of national history indicated that 1% of CIN1, 5% of CIN2 and 12% of CIN3 would progress to invasive cancer (74). Treatment such as surgery or chemo-radiotherapy could cure 80-95% of women with early stage cervical cancer and 60% with advanced stage disease (75).

2.2.1 Screening for cervical cancer

The cervical screening program is regarded as the most successful cancer screening program and has substantially contributed to reduced number of cancer incidence and mortality. The purpose of cervical screening is to reduce cancer incidence by early detection and early treatment of cancer precursors, and to improve the prognosis and to reduce mortality for invasive cancer (76). In Sweden, all women have been invited to organized screening for cervical cancer in a three-year interval (for those at age 23-50 years) or a five-year interval (for those at age 51-60 years) since 1970s. In addition to organized screening, opportunistic screening occurs when women seek for screening service instead of a planned test. The average participation rate in 2016 was around 82% for women who had participated in screening, among which, 70% happened in organized screening (77). The conventional cytology method, that is, the papanicolaou smear test (Pap smear), has been used for cervical screening. The cytological abnormalities determined by Pap smear can be managed by colposcopy, sometimes including a punch biopsy. The cervical screening has significantly improved the cure for cervical cancer. The cure proportion was 92% for screening detected women whereas 66% for symptomatic women (76), mainly due to detection of early stage disease and the asymptomatic

feature of screening detected cases. However, the detection of precancerous lesions in screening might also raise the concern about over-diagnosis and over-treatment, because not all lesions will advance to cancer eventually.

2.2.2 Health outcomes during cervical cancer evaluation

Despite the great health benefits entailed by cervical cancer screening, concerns for potential harms have also been raised. In addition to obstetric outcomes related to treatment procedures, psychological health outcomes might also be of relevance. During the diagnostic workup, women confront not only the fear of having a progressing disease, but also uncertainty of consequence of the disease (78). Due to the sexually transmitted nature of HPV and its link to cervical cancer, women screened with positive result might experience extra anxiety, social stigma, concerns of relationships, and worry of disclosing the result to the others (79). Women receiving an abnormal screening test result were indeed shown to have an increased risk of anxiety, distress, sleep disturbance and poor concentration (80–82). It was also recognized that colposcopy and its related procedures might lead to an increased level of anxiety and other psychological outcomes (80,82). Elevated psychological distress was also noted among women with low grade cytological lesions (83). Most of the previous studies were conducted in selected population and used questionnaires with self-reported information, which might limit the generalizability of their findings. To date, a comprehensive investigation is still lacking in quantifying concrete health outcomes, because patients and clinicians are more likely to underestimate the potential harms in cancer screening (84,85). Moreover, health problems such as bleeding, infection and adverse drug events were reported as a result of invasive diagnostic procedures and treatment (86). To what extent the health burden can be requires more investigations.

2.3 BREAST CANCER

Breast cancer is the most common cancer among women and the fifth cause of death from cancer (87). There was about 2 million breast cancer cases and 601,000 cancer deaths in 2017 around the world (88). About one in eight to ten women will develop breast cancer during their lifetime (89). The median age at diagnosis was 61 (90), and the 5-year relative survival for breast cancer was around 80% (91). In Sweden, 9,382 patients were diagnosed with breast cancer in 2015, leading to an incidence of 192 per 100,000 person-years (67). Thanks to breast cancer screening and the advancement of cancer treatment, the mortality has substantially declined since the 1970s (92). Breast cancer is rare in men. Apart from being a female, the risk of developing breast cancer is highly correlated with advanced age as most breast cancer is diagnosed among women over 50. Mammographic density, referred as the white proportion of the mammogram, is another important risk factor for breast cancer. A systematic review and meta-analysis demonstrated that women with 75% mammographic density have almost five times risk of breast cancer, compared to women with less than 5% mammographic density (93). Abnormalities such as tumor tissues are more difficult to detect on a mammogram in dense breasts. Other risk factors include previous benign breast disease (94), family history (95), risk

genes (96), higher socioeconomic status (97), use of hormonal therapy (98), and alcohol consumption and obesity (99,100).

Breast cancer often originates from cells in the milk-producing ducts (ductal carcinoma), less common in the glandular tissues known as lobules (lobular carcinoma) and in other tissues. Signs of breast cancer include a lump or change in the breast. The routine cancer screening and the improvement in diagnosis have led to an increased detection of early precursor lesions of the breast, including atypical ductal hyperplasia, flat epithelial atypia, atypical lobular hyperplasia and radial scar (101). Ductal carcinoma in situ was rarely diagnosed before 1980, but now accounts for 25% of newly diagnosed breast cancer (101). The certainty about which lesions will progress to cancer needs to be improved. A recent literature review reported 9-28% upgrade rates to breast cancer for different precursor lesions of the breast (102). Surgery is the primary treatment to remove tumor, combined or not combined with other treatments (radiation therapy, chemotherapy, hormone therapy, etc.).

2.3.1 Screening for breast cancer

The purpose of breast cancer screening is to identify breast cancer in early stage, where more treatment options and better treatment outcomes can be achieved. Screening for breast cancer with mammography results in controversial benefits. Although lower mortality rate due to breast cancer was observed after mammography screening (92,103), the debate is still ongoing about risks and benefits (28). Extending the screening age, or with shorter intervals are likely associated with greater mortality reduction and greater health benefits, however studies are yet to quantify the precise magnitude of benefits and the potential harms (104).

In Sweden, women at age 40-69 years have been offered regular mammography screening since 1974 and it became nationwide since 1997 (105). Nowadays, women at age 40-74 years are invited for mammographic screening every 18-24 months, and the participation rate is about 80% (106). In the screening settings, women with suspected imaging on a mammogram are referred for further investigation, usually including a combination of expanded mammographic imaging and ultrasound and when needed with puncture biopsy. Magnetic resonance imaging (MRI) is also possible at times. Despite of the consistent evidence showing the reduced mortality from breast cancer due to screening, the debate is ongoing considering the potential harms of screening with mammography, including false-positive results, negative psychological consequences, and over-treatment of cancers (28).

2.3.2 Health outcomes during breast cancer evaluation

Patients with breast cancer were reported to have a higher prevalence of psychiatric disorders compared to patients with other cancer types (107). Women with a newly diagnosed breast cancer were found to have an increased risk of psychiatric symptoms (108). A recent study reported an increased risk of depression, anxiety, and stress-related disorders among women with invasive breast cancer, with the highest risk increase shortly after diagnosis and remained elevated during five years after diagnosis (109). Apart from patients with invasive breast cancer, patients with *in situ* breast cancer had also an increased risk of stress-related disorders

during six months after diagnosis (109). The results on whether or not women with false positive mammography result have negative psychosocial consequence are controversial. In one study, psychological distress was found to persist for three years (110), whereas others argued that such psychological experience had no adverse effects on psychological functioning (111). Controversial findings were also noted in women receiving a clear result in screening (32,112).

Compared to psychiatric disorders or symptoms, less is known regarding other health risks. A population-based study examined the long-term risk of suicide after diagnosis among breast cancer survivors in the United States, and found the highest risk increase during the first years after cancer diagnosis, although the elevated risk remained 15 years after diagnosis (113). Breast cancer patients have also been shown to have higher risk of cardiovascular death than general population (114,115). It was reported that breast cancer patients had more than 3-fold risk increase of developing venous thromboembolism compared to cancer-free counterparts (116), with particular risk increase in the first year after cancer diagnosis (42). In addition, breast cancer patients had more than 20% increased risk of death and hospital admission due to accidents within five years of diagnosis (53). These findings suggest that the immediate time period after cancer diagnosis is a critical time window for stress-related health problems. Complications, including bleeding and hematomas, infections, and pain, are also recognized in patients receiving a biopsy for cancer diagnosis (117). Given the large number of women suspected for a potential breast cancer, studies are needed to measure the impact of health risks during cancer evaluation process, for all women undergoing a diagnostic workup of potential breast cancer.

2.4 INFLAMMATION – A COMMON PATHWAY OF STRESS-RELATED HEALTH OUTCOMES

Stress response can provoke comprehensive neurochemical, neurotransmitter and hormonal alterations by predominantly activating the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis (118). Recently, inflammation is proposed to be a new and promising biological mechanism linking together stress and stress-related health outcomes(119), providing a new opportunity for disease prevention.

2.4.1 Inflammatory pathway

Stress hormones, such as glucocorticoids, are the major hormones secreted by adrenal glands from HPA axis in stress response, and enhance the activation of immune system (120). The activated inflammatory response and inflammation can serve as a common pathway between stress and its subsequent health outcomes. The increase in proinflammatory cytokines is linked to a variety of symptoms, such as fatigue, anhedonia, cognitive impairment, social withdrawal and motor retardation, which are further associated with sickness behaviors and somatic diseases (121).

Evidence has been accumulated showing an association between inflammation and psychiatric symptoms and disorders. Peripheral inflammation and neuroinflammation could play a pivotal

role in the initiation and progression of mood and psychiatric disorders (122), and among others, cardiovascular diseases (118). For example, activation of the immune system and its influence on the neurodevelopmental process are noted in animal models (123,124) and human studies (125,126). Positive association has been noted between depression and plasma inflammatory markers, with a dose-response relationship (127). Patients hospitalized for infection were found to have a 62% increased risk of mood disorder (122). Furthermore, cytokines are crucial for the normal functioning of the brain, and can intervene neurocircuitry and neurotransmitter systems (128,129). Psychological distress, together with its resultant psychiatric symptoms, might induce behavioral changes (43,130). The increased inflammatory cytokine levels might contribute to the development of depressive symptoms, which might further correlate with cognitive impairment and reduced motivation and motor activity (118,131). As a result, stress-induced cognitive impairment could be associated with risk of injuries, such as hip fracture and falls (132,133). Indeed, using a self-reported neuropsychological test, lower score in cognitive and motor function was found to be associated with the risk of falls among elderly people without dementia or mild cognitive impairment (133). However, these studies were limited to experimental or clinical settings, with highly selected samples. More studies are needed to enroll a larger group of heterogeneous population.

Although the role of inflammatory pathway has been increasingly recognized as a pivotal molecular basis in the pathogenesis of many diseases (118), the mechanisms underpinning stress and stress-related diseases are still under debate.

2.4.2 Anti-inflammatory medication as potential treatment approach

Assuming an important role of inflammatory pathway in linking together stress and stress-related health outcomes, the use of anti-inflammatory agents, such as nonsteroidal anti-inflammatory drugs (NSAIDs), has been proposed as a potentially effective therapeutic strategy for stress-related health outcomes (134,135). The therapeutic potential of NSAIDs might involve cyclooxygenase (COX) enzymes including COX-1 and COX-2, which are essentials for prostaglandins involved in inflammation.

NSAIDs are a variety of drugs with analgesic, anti-inflammatory and anti-pyretic effects (136). The potential utility of NSAIDs on stress-related health outcomes is still under debate. In one study, the outcome of major depressive disorder was not improved after use of NSAIDs (137). In another study, a decreased rate of incident depression was noted after continued use of low-dose aspirin, while an increased rate was noted after the use of non-aspirin NSAIDs and high-dose aspirin (138). Notably, a meta-analysis of randomized clinical trials suggested a promising effect of NSAIDs in reducing major depressive disorder by inhibiting proinflammatory cytokines, without increasing risks of adverse effects such as gastrointestinal and cardiovascular events (134). In addition to the conflict findings of aspirin use and cancer mortality (139,140), there remains a need to investigate the potential of aspirin and non-aspirin NSAID use on deaths from non-cancer causes.

3 AIMS

The overarching aim of this thesis was to contribute to a comprehensive picture of health risks in relation to cancer diagnostic workup, by examining 1) risks of stress-related health outcomes related to the cancer diagnostic workup, and 2) the potential effect of anti-inflammatory medication use in modulating the excessive risks of stress-related health outcomes following a cancer diagnosis.

Specifically, we aimed:

- To examine the risk of hospitalization for injuries immediately before and after cancer diagnosis (Study I).

- To examine the risk of hospitalization for injuries during the diagnostic workup of cervical cancer and its precursors (Study II).

- To examine the risks of psychiatric disorders and cardiovascular diseases during the diagnostic workup of potential breast cancer (Study III).

- To examine the association between use of NSAIDs and the risk of unnatural death due to suicide or accidents following a cancer diagnosis (Study IV).

4 STUDY MATERIALS

4.1 SWEDISH POPULATION AND HEALTH REGISTERS

Data used in each individual study was based on a variety of Swedish population and health registers.

Swedish Cancer Register

The Swedish Cancer Register includes all diagnoses of malignant tumors and certain benign tumors in Sweden since 1958. It is regulated by law that all healthcare providers must report any newly identified cancer to the register. The reporting to Cancer Register is commonly notified twice by physicians and pathologists separately to double confirm the cases. The completeness and reliability of cancer registration in the register is verified to be nearly 100% (141). Since 2004, the information on histology and tumor stage is largely available in the register.

Swedish Cause of Death Register

The Swedish Cause of Death Register collects nationwide information on all death certificates nationwide from 1961 onward, including dates and the underlying and contributing causes of death. It is compulsory to report all deaths to the register by law (142), by physicians in hospitals or medical examiners if death occurs outside of hospital. The causes of death have been validated with high accuracy and are considered as a valuable resources for medical research (142).

Swedish Patient Register

The Swedish Patient Register collects hospital discharge records with a coverage of 60% across the country since 1964/1965, and become 100% nationwide since 1987 (143). This register includes further outpatient visit from 2001 onward, with a coverage above 80% (143). Information such as admission and discharge dates, primary and secondary discharge diagnoses coded according to the International Classification of Disease (ICD) system, has been provided in the register. All diagnoses were coded according to the 7th Swedish revision of ICD codes (ICD-7 before the year 1969), in ICD-8 (1969 to 1986), in ICD-9 (1987 to 1996), and in ICD-10 (from 1997-). This register has been validated for a variety of diseases and is considered as a reliable source for research use. In the Patient Register, diagnoses of injuries are mandatory to be reported with corresponding external causes, and the completeness of such information is above 90% (143).

Swedish Prescribed Drug Register

The Swedish Prescribed Drug Register contains information on all prescribed and dispensed medications from all Swedish pharmacies from July 2005 onward (144). It includes information on medicine types, prescription and dispensing dates, quantity, defined daily dose, and prescription text updated for each dispense (144). All medicines recorded in the register

have been classified according to the Anatomical Therapeutic Chemical (ATC) system (145). Prescription for medication use is commonly renewed once a year and dispensed for up to a three-month supply in Sweden. The implementation of this prescribed drug register has been regarded as a great opportunity to explore effectiveness of drug use on various health risks.

Other population registers

The Total Population Register is regularly updated by Statistics Sweden (SCB). It includes information on date of birth, socioeconomic status, cohabitation status, registered address, migration and death for all residents from 1960s (146). A national population and housing census was conducted every five or ten years through questionnaires, collecting information on employment, household composition and accommodation until 1995, which was then replaced by a completely register-based approach (147). The Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA in acronym) has collected information on cohabitation status, income, employment and education from labor market, educational and social sectors for all residents at age 16 and above in Sweden, and is updated every year since 1990. Same information can also be obtained from other registers, for instance, education level from the Education Register.

4.2 SWEDISH NATIONAL CERVICAL SCREENING REGISTRY (NKCX)

Cervical screening was organized and implemented on county level in Sweden in late 1960s. The NKCx is a quality register for cervical cancer prevention. It has since the 2002 saved all data on screening test and diagnostic results across the country. Large part of screening test results is from planned test for healthy women for screening purpose, and data is also included for women with suspected changes under investigation. The NKCx comprises information including cytology test results from Pap smears, histology results from punch biopsies, and treatments for those in need (148). The coverage of cytology tests increased over time and reached almost 100% in 1993; a full coverage of histology tests was also achieved in 1993 (148).

4.3 SKÅNE HEALTHCARE REGISTER (SHR)

Skåne is the southernmost region in Sweden, covering about one-eighth of the Swedish total population (~1.3 million residents) (149). All individuals residing in this region can actively choose to be enrolled in a primary care center, or automatically be assigned to the nearest primary care center according to residential area. All medical records have been entered by healthcare providers and automatically transferred to the Skåne Healthcare Register (SHR) since 1998. The SHR includes data from all levels of healthcare (either public/private sectors, primary, specialist or hospitalizations), including type of healthcare professional, date of visit, diagnostic codes, and surgical or non-surgical codes. The coverage is around 100% for inpatient care, and has increased to over 90% for secondary outpatient care after 2010 (150). The proportion of physician visits in primary care with an assigned diagnosis was approaching 100% over time (Figure 4.1). The accuracy of recorded diagnoses was validated and considered

to be of good quality for research (150). Healthcare provided outside Skåne for residents in this region usually requires restricted permission and is believed to be at a negligible level.

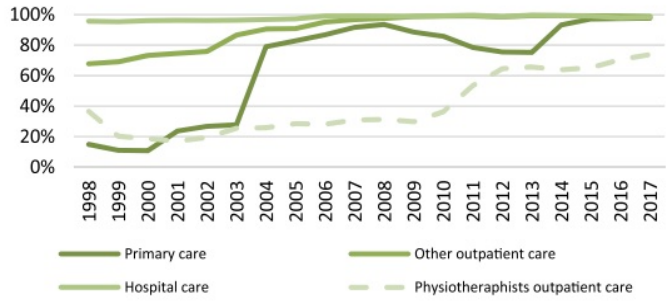


Figure 4.1 Proportion of physician visits that have an assigned diagnosis, 1998-2017 (150).

Table 4 Overall view of registers used in studies.

Register	Source	Content	Study
Swedish Cancer Register	Socialstyrelsen	Cancer diagnosis	Study I, II, III, IV
Swedish Cause of Death Register	Socialstyrelsen	Death	Study I, II, III, IV
Swedish Patient Register	Socialstyrelsen	Clinical diagnosis	Study I, II, IV
Total Population Register	SCB	Total population, migration	Study II, III
Swedish Education Register	SCB	Education level	Study I
Swedish population and housing census	SCB	Cohabitation status, occupation, region of residence	Study I
The Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA)	SCB	Education, income, cohabitation status	Study IV
Prescribed Drug Register (PDR)	Socialstyrelsen	Dispensed medication	Study IV
Swedish National Cervical Screening Registry	NKCx	Cervical screening	Study II
Skåne Healthcare Register (SHR)	Region Skåne	All levels of healthcare visits in Skåne	Study III

4.4 ETHICAL CONSIDERATION

Our register-based studies largely relied on information retrieved from population and health registers, which raised the concern of how to protect sensitive data, such as medical records and personal information. According to Swedish regulation, informed consent from each individual is not required for research purposes when using national registers, given that an ethical permit is granted by ethical review board upon study initiation (151). All studies include in this thesis were approved by the Regional Ethical Review Board in Stockholm (EPN 2015/1574-31). The informed consent from individual level was therefore waived in all studies.

The personal identification number (PIN) is uniquely assigned by the Tax Agency to each resident after birth or immigration. The PIN was replaced by a study-sensitive identifier during data linkage conducted by the National Board of Health and Welfare and Statistics Sweden. All linked data were delivered under strict protection and stored safely on server in the host institution with limited access. Moreover, research findings are communicated on aggregated level, in tables, figures and text. No case was individually discussed. Therefore, sensitive data was anonymous and handled safely during the entire research process.

5 STUDY DESIGN AND METHODS

5.1 INJURIES AROUND CANCER DIAGNOSIS (STUDY I)

5.1.1 Study design and participants

Based on the Swedish Cancer Register, we identified in total 740,114 individuals with a first cancer diagnosed between 1991 and 2009. All cancer patients were cross-linked to the Swedish Cause of Death and Patient Registers by using the uniquely assigned PIN to all Swedish residents. We classified all cancer patients into common cancer types by using the 7th Swedish revision of ICD codes. Smoking and drinking alcohol are two lifestyle factors that are related to both the risks of cancer and injuries (152,153). We therefore additionally classified cancers of mouth, nasopharynx, oesophagus, pancreas, lung, kidney, bladder and urinary tract as smoking related cancers, and classified cancers of mouth, larynx, oesophagus, biliary duct and liver as alcohol related cancers.

Table 5.1.1 Numbers of cancer patients according to cancer types.

Cancer types	ICD-7	Number of individuals
any cancer	140-209	740,114
prostate cancer	177	123,837
breast cancer (female only)	170	101,458
colorectal cancer	153,154	84,527
non-melanoma skin cancer	191	33,409
lymphatic and hematopoietic cancer	200-207	52,266
lung cancer	162, 163	49,491
cancers of central nervous system	193	21,199
“severe cancers” including cancers in oesophagus, liver, and pancreas	150,155,156,157	220,087
smoking related cancers	140,141,150,157,180,181,143-149,160-162	116,501
alcohol related cancers	141,155,161,143-146,148-150	29,511

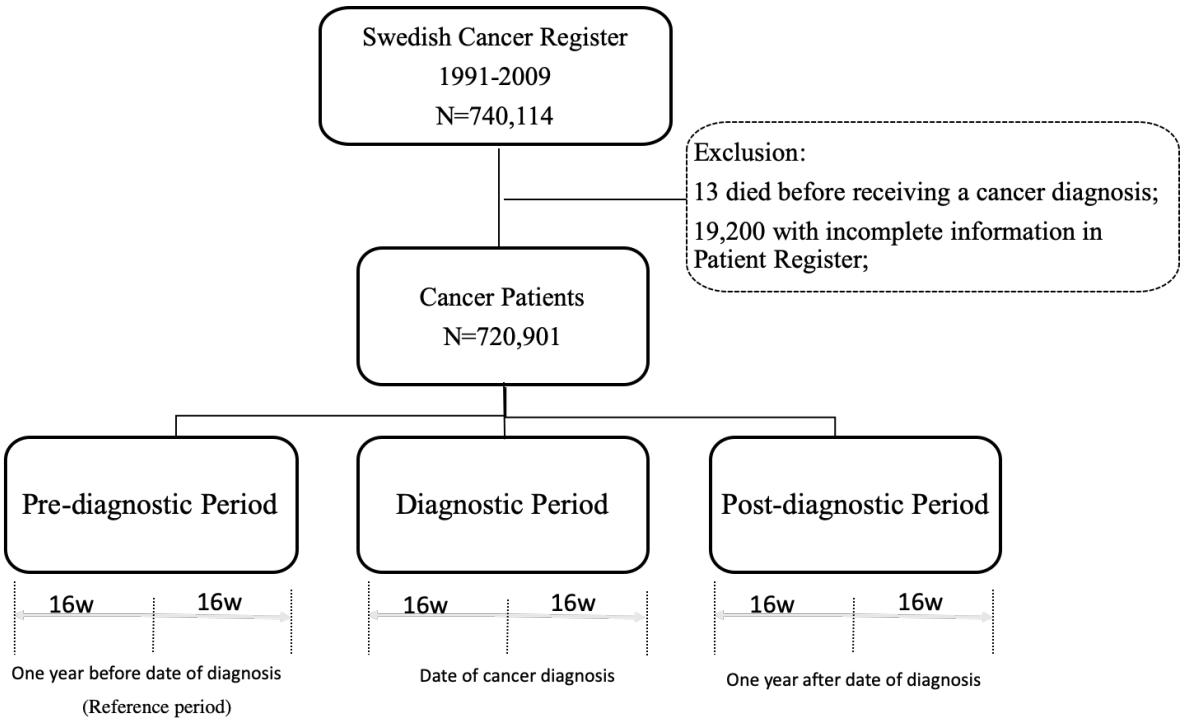


Figure 5.1.1 The flowchart and design of Study I.

5.1.2 Definitions of time periods

The Swedish Cancer Register provides no information on the start of clinical evaluation for a cancer. However, it was reported that the median waiting time from the first referral to a specialist for suspected cancer and the primary treatment, was around two months during the study period in Sweden (18). The waiting time varied largely between different cancer types. Because the initial contact with healthcare provider, as well as the symptoms of cancer, likely start much earlier than the first specialist visit, we therefore defined the *diagnostic period* as the time interval from 16 weeks before to 16 weeks after the date of cancer diagnosis, presumably covering the routine cancer diagnostic process through the primary treatment in Sweden. We defined the same 32 weeks one year before date of cancer diagnosis as the reference period ("*pre-diagnostic period*"). To compare with the risk increase after diagnosis, we further defined the same 32 weeks one year after date of cancer diagnosis as the *post-diagnostic period*, among patients that were alive one year after diagnosis (N=581,954).

To eliminate the shared risk factors between cancer and injuries, in this study, we used a within-individual comparison design, namely to compare the risk of injuries during the *diagnostic period* or *post-diagnostic period* with the risk during the *pre-diagnostic period* prior to cancer diagnosis, for the same patient.

5.1.3 Ascertainment of injuries

Injuries were ascertained using ICD codes in two ways: 1) "injury diagnosis codes" which describe the body and nature of an injury, and 2) "external cause of injury codes, or E-codes" which describe the cause and intent of an injury (154). The E-codes were first developed in

ICD-9, as a supplementary classification, and were intended to be used in addition to "injury diagnosis codes". The E-codes should provide additional information on multiple conditions, classifying the cause of injury based on the environmental events, circumstances and other adverse effects (155).

In Study I, all hospitalized injuries during the *pre-diagnostic*, *diagnostic* and *post-diagnostic periods*, were identified from the Swedish Patient Register using ICD-9 (1991-1996) and ICD-10 (1997-2010) codes. We separated iatrogenic and non-iatrogenic injuries by using both the injury diagnosis codes and E-codes, throughout the analyses. Injuries related to medical actions (diagnosis, treatment, etc.) or other medical complications were referred to as iatrogenic injuries. Other injuries that were not associated with medical procedures or health seeking behaviors of the patients, were designated as non-iatrogenic injuries. We further classified iatrogenic injuries into drug-related and medical intervention-related injuries. Non-iatrogenic injuries were classified by nature, region, mechanism, place of occurrence, and manner of intent, according to the injury diagnosis codes or E-codes. The ICD codes used for the classification are listed in Table 5.1.2.

Repeated events of injuries were taken into account because one patient could contribute multiple times the diagnoses of injuries. We therefore considered consecutive hospital discharges within one week, or with the same injury diagnoses, as one injury event (18.7%). Because fatal injuries were not possible during the pre-diagnostic period by study design, we excluded from the analysis all injuries with a death record identified at the time of hospital discharge.

Table 5.1.2 Injury classification.

	ICD-10			ICD-9	
	Diagnosis code	**E-code**		**Diagnosis code**	**E-code**
Any Injury	S00-T98	V01-Y98		800-999	(E)807-(E)999
Iatrogenic Injury	1. Drug or biological substances; 2. Medical procedures and care; 2.1 Hemorrhage or hematoma; 2.2 Accidental puncture/rapture of wound; 2.3 Infection; 2.4 Prosthetic device, implant, and graft; 2.5 Unspecified and others;				
Non-Iatrogenic Injury					
1. By nature of injury;	1.1 Fracture 1.2 Contusion or superficial 1.3 Open wound 1.4 Internal organ injury 1.5 Effect of foreign body entering orifice 1.6 Dislocation 1.7 Others				
2. By region of injury;	2.1 Upper extremity 2.2 Head and neck				

	2.3 Lower extremity 2.4 Trunk 2.5 Others
3. By mechanism of injury;	3.1 Fall 3.2 Struck by or against 3.3 Transport 3.4 Nature,animal,plant 3.5 Cut or pierce 3.6 Poisoning 3.7 Others
4. By place of occurrence;	4.1 Residential areas 4.2 Transportation area/Street and highway 4.3 Sports and athletics area 4.4 School, other institution and public administrative area 4.5 Others
5. By manner of intent;	5.1 Unintentional (accidents) 5.2 Intentional self-harm 5.3 Assault 5.4 Undertermined and others

5.1.4 Statistical analyses

We first calculated the incidence rates (IRs) of outcomes, i.e., iatrogenic and non-iatrogenic injuries during *pre-diagnostic*, *diagnostic* and *post-diagnostic periods* among all patients, using the number of injury events divided by accumulated person-months at risk. The time spent in hospital (i.e. days from admission to discharge for each hospitalization), regardless of discharge diagnosis, was not counted as time at risk. To perform a within-individual comparison, we used conditional Poisson regression to estimate the incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for the risks of injuries, by comparing the IRs during the *diagnostic and post-diagnostic periods* with the IRs during the *pre-diagnostic period*, of the same patient (156). IRRs were calculated for cancer patients altogether and by cancer subgroups. For all cancer patients together, we separately estimated the IRRs for every two-week period during the *diagnostic and post-diagnostic periods*. We additionally estimated the associations for different subtypes of iatrogenic injuries and non-iatrogenic injuries.

5.2 INJURIES IN RELATION TO DIAGNOSTIC WORKUP OF CERVICAL CANCER (STUDY II)

5.2.1 Study design and participants

We identified in total 3,016,307 women who were born in Sweden during 1912-1990 and were 18 years and above during 2001-2012. We used uniquely assigned PIN to link all these women to the NKCx, Cancer Register, Patient Register, Total Population Register and Cause of Death Register. After linkage, all women were individually followed from 1st of January or their 18th birthday, until a diagnosis of CIN3 or invasive cervical cancer, a diagnosis of any other cancer, a total hysterectomy, emigration, death, or the end of study period (December 31st 2012), whichever came first.

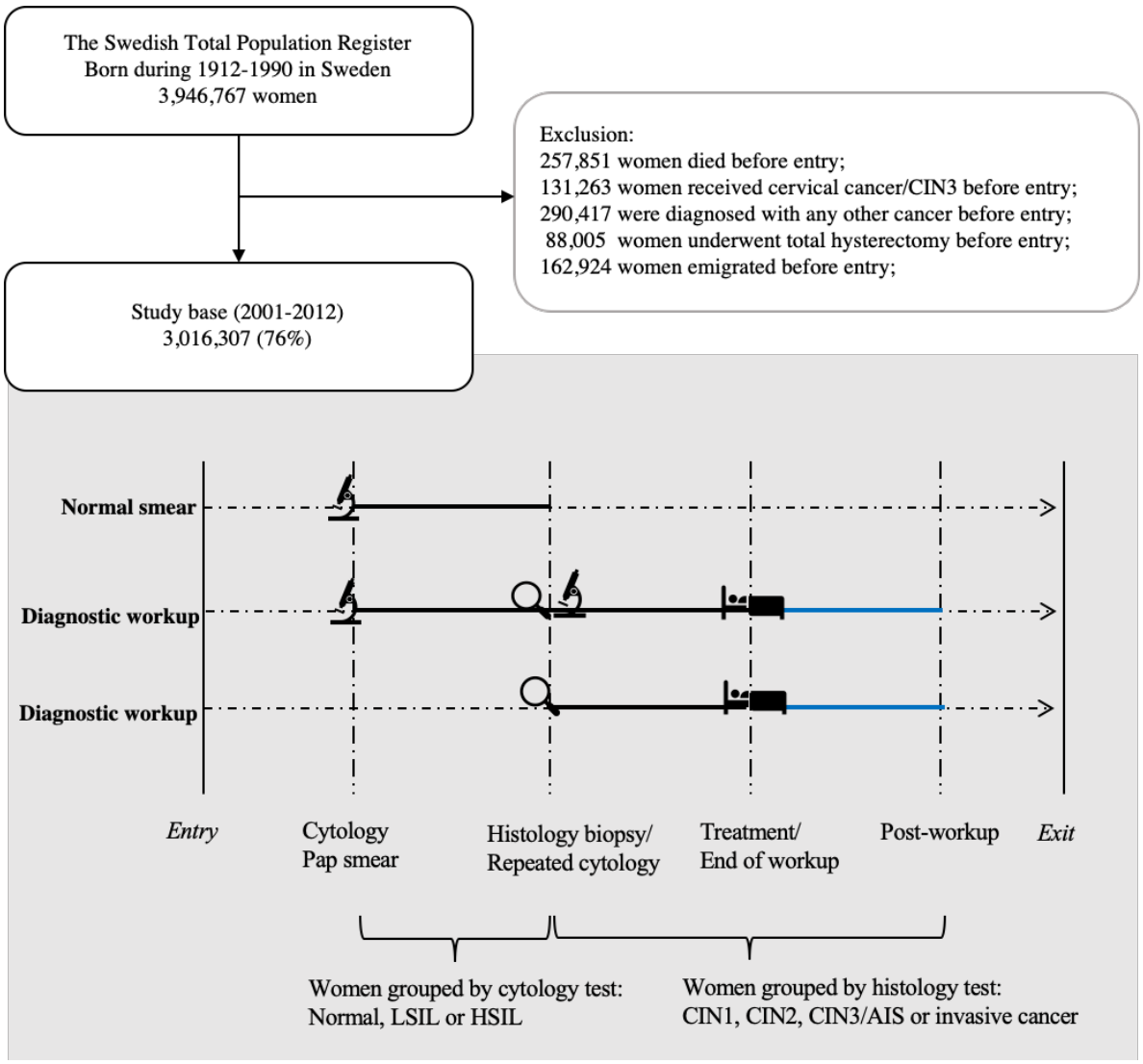


Figure 5.2.1 The flowchart and design of Study II.

5.2.2 Definitions of diagnostic workup

The diagnostic procedures of cervical cancer and its precursor lesions during the study period commonly include cytology test by Pap smear and histology test by punch biopsy. It usually takes 4-6 weeks for the cytological findings to be delivered to a woman after taking a smear. The diagnostic workup for women with "normal smear" was defined as a two-month period starting from the day when a smear was taken, i.e. the waiting time for a normal smear result. The diagnostic workup for women with a diagnosis of invasive cervical cancer and its precursor lesions was defined as the time interval between the first smear or punch biopsy (start of workup) and surgical treatment if surgically treated or two months after the latest smear or biopsy if not treated surgically (end of workup).

Sometimes women could be managed differently based on screening findings or symptoms, and not every woman undergo all diagnostic procedures. For example, women with mild cytological lesions can be managed by repeated smears without punch biopsy, and women with

symptoms can be directed to take punch biopsy without taking smears. Therefore, we categorized women during each diagnostic procedure based on their test results. All women included in this study were classified as unexposed group (women with normal smear) or exposed group (women with a diagnostic workup of cervical abnormalities). We separately studied the time interval between cytology and histology by classifying women according to cytological results (LSIL or HSIL), and between histology and treatment by classifying women according to histological results (CIN1, CIN2, CIN3/AIS (adenocarcinoma *in situ*), or invasive cancer). To contrast the risk of injuries during diagnostic procedures to therapeutic procedures, we further defined a six-month time period after surgical treatment for women treated surgically, and defined a six-month time period after end of diagnostic workup for untreated women as the post-workup period (Figure 5.2.1).

5.2.3 Ascertainment of injuries

The outcomes of interest in this study were hospitalized iatrogenic and non-iatrogenic injuries, identified from the Swedish Patient Register. We used the main discharge diagnosis ICD-10 codes S00-T98, and the external causes E-codes V01-Y98, to identify injuries. Because women can be referred to outpatient and overnight inpatient care for temporary discomfort after punch biopsy, we therefore included only iatrogenic injuries with at least two days of hospital admission as outcomes of interest. Repeated events were taken into account, except for consecutive events with the same primary diagnosis or within one week of each other, which were considered as the same event.

5.2.4 Statistical analyses

We described the characteristics of unexposed and exposed women by histology diagnosis. The differences in age, calendar period (2001-2004, 2005-2008 and 2009-2012), screening adherence, highest education level, income and cohabitation status between unexposed and exposed women were calculated using Pearson's Chi-square test. We calculated crude IRs using numbers of injury events divided by accumulated person-months at risk, discarding days spent during hospital admission. We calculated crude IRs of iatrogenic injuries that required at least two days of admission and hospitalized non-iatrogenic injuries during the two months after a normal smear among unexposed women, and during the diagnostic and post-workup period of the exposed women. We further estimated the IRRs and 95% CIs by comparing the IRs of the exposed women with the IRs of the unexposed women, using Poisson regression. To examine the risk of injuries in relation to specific diagnostic procedures in comparison to therapeutic procedures, we calculated IRs and IRRs separately, between cytology and histology, between histology and treatment (or end of workup), and during post-workup period. All estimates were adjusted for age at smear taking or diagnosis, calendar period, screening adherence, education, income and cohabitation status.

Screening adherence was calculated as the percentage of the actual participation times of cervical screening divided by recommended participation times according to the screening guideline (157). Registered smears beyond screening age were not counted in this calculation.

Because socioeconomic status and cohabitation status were associated with patients' health seeking behaviors (158), we retrieved information from LISA on the highest education level, individualized disposable income, and cohabitation status.

5.3 PSYCHIATRIC DISORDERS AND CARDIOVASCULAR DISEASES DURING DIAGNOSTIC WORKUP OF BREAST CANCER (STUDY III)

5.3.1 Study design and participants

By linking the Total Population Register to Cancer Register and SHR using PIN, we performed a cohort study following all women (N=608,140) residing in Skåne from January 1st, 2005 or 18th birthday, whichever came later, until December 31st 2014, death, diagnosis of breast cancer, diagnosis of any other cancer, total mastectomy, or emigration out of Skåne, which occurred first.

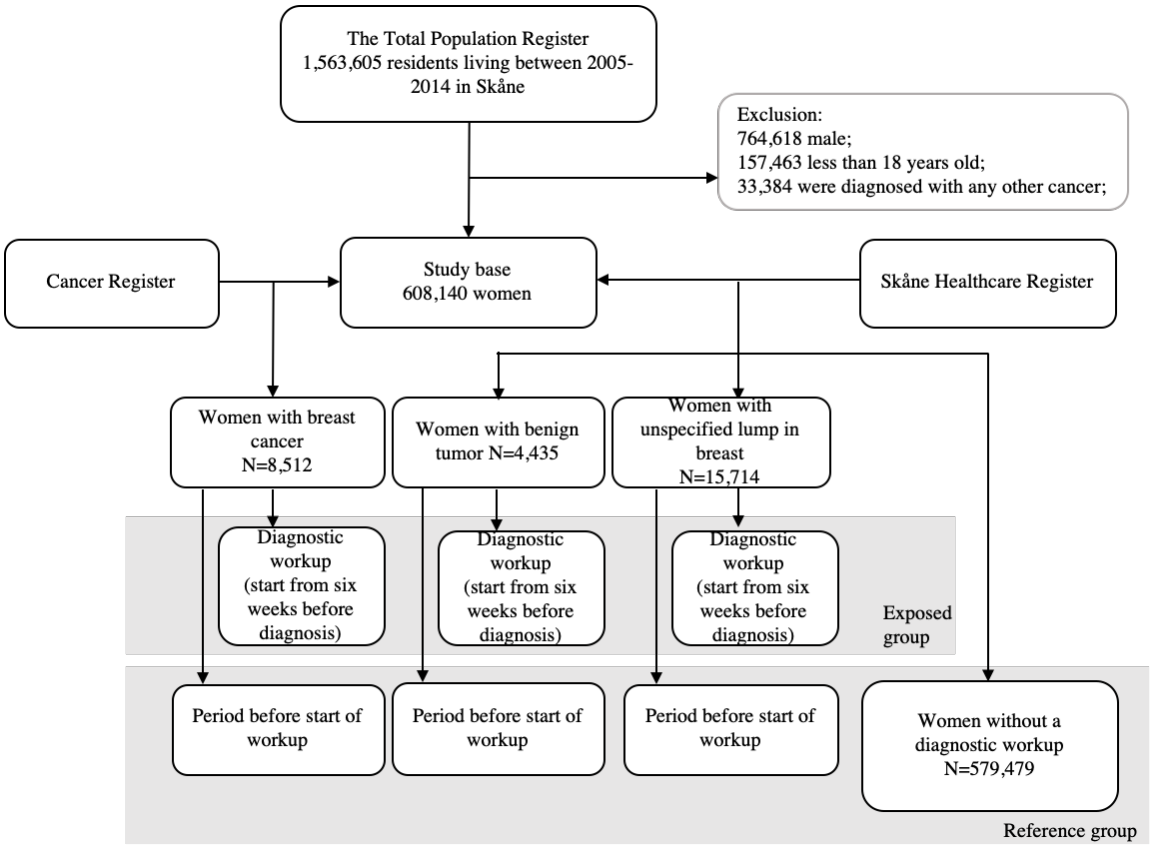


Figure 5.3.1 Flowchart and design of Study III, a population-based cohort study during 2005-2014 in Skåne, Sweden.

5.3.2 Definition of a diagnostic workup

We identified three groups of women as exposed to a diagnostic workup of potential breast cancer that were exclusive to each other.

1) Breast cancer (N=8,512): all women received a first diagnosis of breast cancer during study period and identified from the Cancer Register.

2) Benign tumor (N=4,435): patients with a benign tumor in breast experience a similar diagnostic process as breast cancer patients until receiving a definite diagnosis. Among women without a breast cancer diagnosis, we identified all patients with a primary diagnosis of benign tumor in breast or breast cancer *in situ* from the Cancer Register and SHR. We referred to this group as "benign tumor", due to the fact that 98.7% patients in this group had a diagnosis of benign tumor.

3) Lump in breast (N=15,714): unspecified lump in breast is one of the most common symptom for breast cancer patients and it is often the reason to start a breast diagnostic workup. Among women without a diagnosis of breast cancer or benign tumor in breast or breast cancer *in situ,* we identified women with unspecified lump in breast from SHR.

We had no information in the register regarding the course of diagnostic workup of potential breast cancer. According to the national cancer care program, the median waiting time from a well-founded suspicion for a potential breast cancer until start of initial treatment was 42 days for 80% of breast cancer patients in Skåne (159). To validate the waiting time before diagnosis using data from SHR, we counted number of healthcare visits during each week before diagnosis among women with breast cancer, and compared the number of visits per week to the week before. As a result, we found that women started to have increased number of healthcare visits from the 6th week before diagnosis. Therefore, the start of diagnostic workup of potential breast cancer was defined as from the 6 weeks before diagnosis.

Apart from women that had a breast diagnostic workup, women who did not have a breast diagnostic workup during the follow-up were considered as reference (N=579,479). Women who underwent a breast diagnostic workup contributed also their person-time to the reference group before the start of workup (Figure 5.3.1).

5.3.3 Ascertainment of psychiatric disorders and cardiovascular diseases

We used ICD-10 codes I00-I99 to identify all diagnoses of cardiovascular diseases and F10-F99 for all diagnoses of psychiatric disorders from SHR and considered them as the primary outcomes of interest. We included deaths due to cardiovascular diseases from the Cause of Death Register that were not preceded by a related hospital visit according to SHR, as additional outcomes of cardiovascular diseases. Repeated outcomes were included except for subsequent events with the same diagnosis and occurred within one month of each other. We further classified psychiatric disorders as stress reaction or adjustment disorder, depression, anxiety, substance abuse and others. Cardiovascular diseases were grouped into myocardial infarction, hypertensive diseases or aneurysm of the heart, embolism or thrombosis, stroke and other diseases of the circulatory system.

5.3.4 Statistical analyses

We calculated the crude incidence rates (IRs) of psychiatric disorders and cardiovascular diseases for reference group and during the six weeks before diagnosis for all exposed women, by dividing the number of outcome events with the accumulated person-months at risk. We

used Poisson regression to estimate the IRRs and 95% CIs, by comparing the IRs of the exposed women with the IRs of the reference group. Because outcome events were measured repeatedly, we used a clustered sandwich estimator to control for the intra-individual correlation. The underlying timescale in analysis was attained age. All estimates were additionally adjusted for cohabitation status, registered parish as a proxy for socioeconomic status (both ascertained from the Total Population Register), and pre-existing psychiatric disorder or cardiovascular disease (ascertained from SHR). Status on pre-existing psychiatric disorders or cardiovascular diseases was updated at the start of each time period, to account for the time-varying nature of these variables.

Because the association might differ for a breast diagnostic workup initiated due to symptoms compared to a workup initiated by screening findings, we conducted the same analysis separately for workups due to screening and due to symptoms, during 2009-2014, when such information on breast cancer screening was largely available in SHR.

5.4 NSAID USE AND UNNATURAL DEATHS AFTER CANCER DIAGNOSIS (STUDY IV)

5.4.1 Study design and participants

Due to the availability of data on dispensed medication since 1 July 2005 in the Sweden Prescribed Drug Register, we identified in total 403,322 patients with a newly diagnosed cancer between October 2005 and December 2014 from the Swedish Cancer Register. Using the uniquely assigned PIN to all residents in Sweden, all patients were cross-linked to different registers to obtain personal information on death (from the Swedish Cause of Death Register) and emigration (from the Total Population Register). After excluding patients who died (N=155) and emigrated (N=14,724) before cancer diagnosis, 388,443 patients were followed from the date of cancer diagnosis, until emigration, death, or December 31, 2014, whichever came first.

5.4.2 Definitions of medication periods

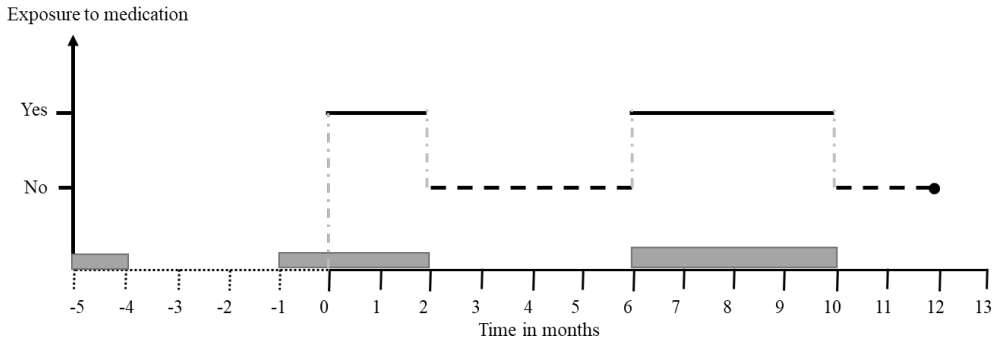
In Sweden, low-dose aspirin cannot be purchased over-the-counter without a prescription, we therefore focused on aspirin with a daily dose of 75 or 160 mg. From the Swedish Prescribed Drug Register, patients who had medication dispensed with ATC codes B01AC06, B01AC30 and B01AC56 were considered as medicated with low-dose aspirin, and with ATC codes starting with M01A were considered as medicated with non-aspirin NSAIDs.

We identified all aspirin and non-aspirin NSAIDs dispensed between three months before cancer diagnosis and the end of follow up, for each cancer patient. We summed up the multiple prescriptions at the same dispense date for the same drug, and detracted any unused drug that was returned to the pharmacies from the total amount. To construct the on- and off-medication periods for each patient during follow-up, we took advantage of the dispense date and the prescription text updated for each prescribed medication. Days on medication can be estimated from the prescription text of the dispensed drug. Because the defined daily dose does not

necessarily correspond to the recommended or prescribed daily dose, we estimated the time on medication as the division of the total amount of dispensed drug by the prescribed daily dosage for medication per medicated period, for each patient. The prescribed daily dosage for each medicated period was largely extracted from the prescription text. The defined daily dose was used only when the prescription text was not available.

Therefore, the on-medication period was defined as the time interval from the most recent dispense date of aspirin or non-aspirin NSAIDs, until the last day when specific NSAID was estimated to be consumed. Time periods outside on-medication periods among patients who had ever used NSAIDs, and all time periods during follow-up of patients who did not use any NSAID, were defined as off-medication periods (Figure 5.4.1).

Figure 5.4.1. Illustration of on- and off-medication periods during follow-up using one fictitious patient as an example*



*Solid line of axis "time in months" is follow-up time. Dot line of axis "time in months" is the time before follow-up. Patient starts to be at risk from time 0 and onwards. Gray box represents on-medication period, and filled circle stands for occurrence of failure or censoring.

5.4.3 Ascertainment of unnatural deaths

We used the ICD-10 codes X60-X84, V01-X59 and Y85-Y86 to ascertain deaths by suicide or accidents. Death due to accident was further classified as death due to transport accident, fall, accidental threat to breathing, unspecified fracture, or others.

Table 5.4.1. Classification of unnatural deaths.

Unnatural death	ICD-10
Death due to suicide	X60-X84
Death due to accident	V01-X59, Y85-Y86
- transport accident	V01-V99
- fall	W00-W19
- accidental threats to breathing	W65-W84
- unspecified fracture	X590
- others	W20-W64, W85-W99, X00-X58, X599, Y85-Y86

5.4.4 Statistical analyses

We used Cox proportional hazards regression model to estimate the hazard ratios (HRs) and 95% CIs of suicide and death due to accident after cancer diagnosis, by comparing the on-

medication periods with the off-medication periods of aspirin and non-aspirin NSAIDs. Population attributable fraction (PAF) is defined as the fraction of cases in population that can be attributable to a specific exposure (160). We estimated PAF to measure the size of unmedicated population that was affected due to a lack of exposure (161). We also separately assessed the association by major causes of death due to accident. In all regression models, we used time since cancer diagnosis as the underlying timescale, and additionally adjusted the estimates for age at diagnosis (continuous variable), sex, cancer type, cancer stage (localized limited, localized advanced, regional spread, distant metastasis, unknown, or not applicable), highest education level, occupation, cohabitation status, pre-existing psychiatric disorders, chronic disease score (continuous variable), and calendar year of diagnosis.

Information on the highest education level, occupation, and cohabitation status was retrieved from LISA. We defined pre-existing psychiatric disorders as having any inpatient or outpatient hospital visit for psychiatric disorders from 1987 until the date of cancer diagnosis, and updated such information for each period (ICD-9 codes 290-319, and ICD-10 codes F10-F99). Chronic Disease Score was a measure of comorbidity based on the prescribed medications dispensed for each patient, after excluding anxiolytics, antidepressants, and antipsychotic and anti-inflammatory medications.

6 RESULTS

6.1 INJURIES AROUND CANCER DIAGNOSIS (STUDY I)

Iatrogenic injuries

We identified in total 7,306 iatrogenic injuries during the diagnostic period of all cancer patients, corresponding to an IR of 0.60 per 1,000 person-months. We found a statistically significantly increased rate of iatrogenic injuries among patients with all cancers during both diagnostic and post-diagnostic periods. The rate increase was more pronounced during the diagnostic period (IRR 7.0; 95% CI, 6.6 to 7.4), than post-diagnostic period (IRR 3.5; 95% CI 3.3 to 3.8), compared to the pre-diagnostic period. The rate increase was higher during diagnostic period than post-diagnostic period for all cancer types. Patients with cancers of the central nervous system were at greatest rate increase of iatrogenic injuries, and patients with non-melanoma skin cancer had the smallest rate increase, during diagnostic period (Figure 6.1.1).

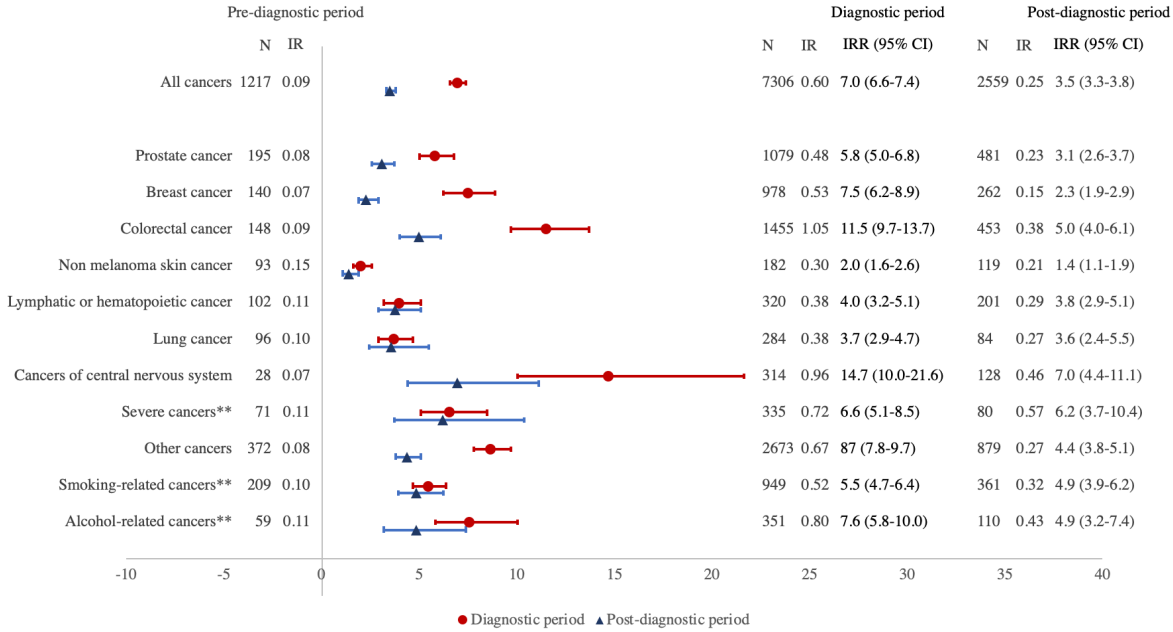


Figure 6.1.1 Incidence rates (per 1,000 person-months) and incidence rate ratios of iatrogenic injuries during the diagnostic period and post-diagnostic period, compared to the pre-diagnostic period, among 720,901 cancer patients diagnosed during 1991-2009 in Sweden*

** Severe cancers include cancers of esophagus, liver, and pancreas. Smoking-related cancers include cancers of mouth, nasopharynx, esophagus, pancreas, lung, kidney, bladder and urinary track. Alcohol-related cancers include cancers of mouth, larynx, esophagus, biliary duct and liver.

During the diagnostic period, the IRRs of iatrogenic injuries started to increase from two weeks before cancer diagnosis and peaked within the first two weeks after cancer diagnosis (IRR 48.6; 95% CI, 37.3 to 63.5). The magnitude of rate increase was smaller thereafter but remained statistically significant during the entire diagnostic period (Figure 6.1.2). In contrast, the rise in the rate of iatrogenic injuries was found to be smaller and decreased monotonically throughout

the post-diagnostic period (Figure 6.1.2). During the diagnostic period of all cancer patients, the greatest rate increase was observed for infection, wound complications, and bleeding. (Figure 6.1.3)

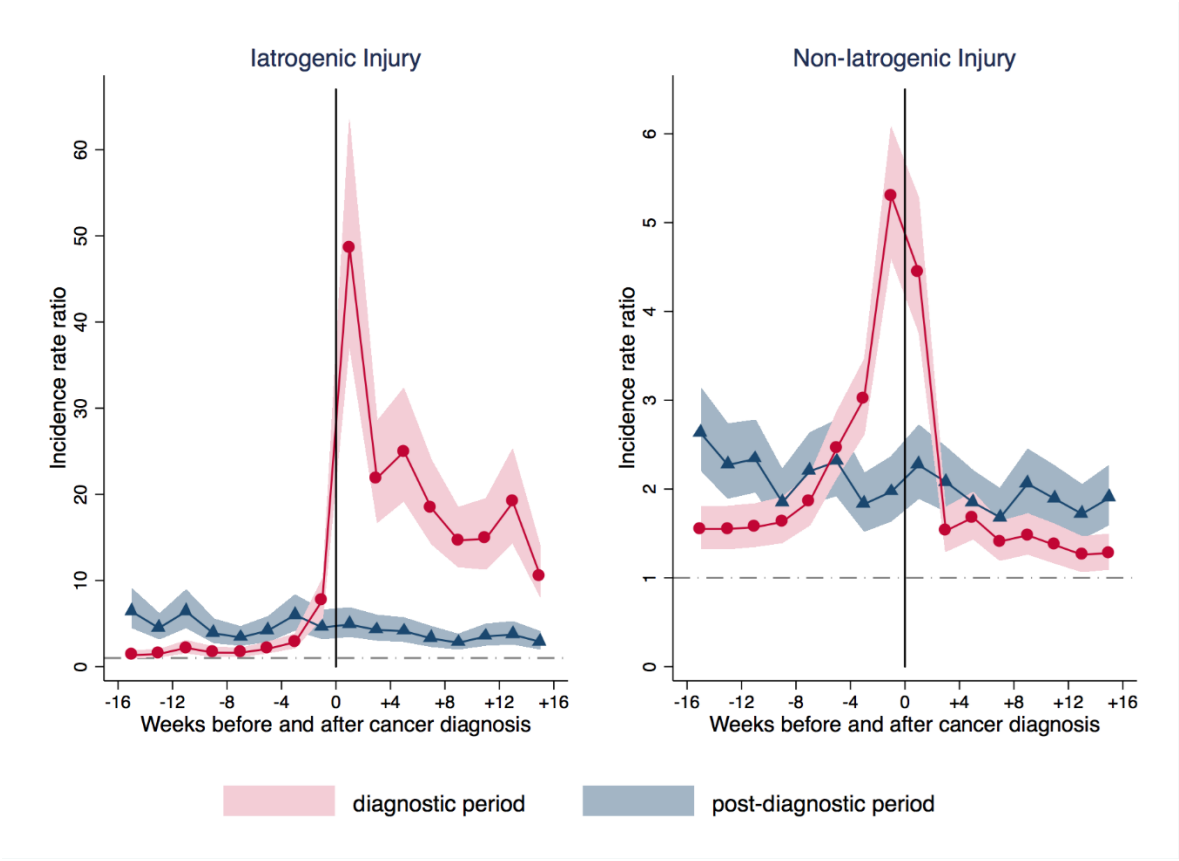


Figure 6.1.2 Incidence rate ratios and 95% CI of injuries during the diagnostic period and post-diagnostic period, compared to the pre-diagnostic period, among 720,901 cancer patients diagnosed during 1991-2009 in Sweden.

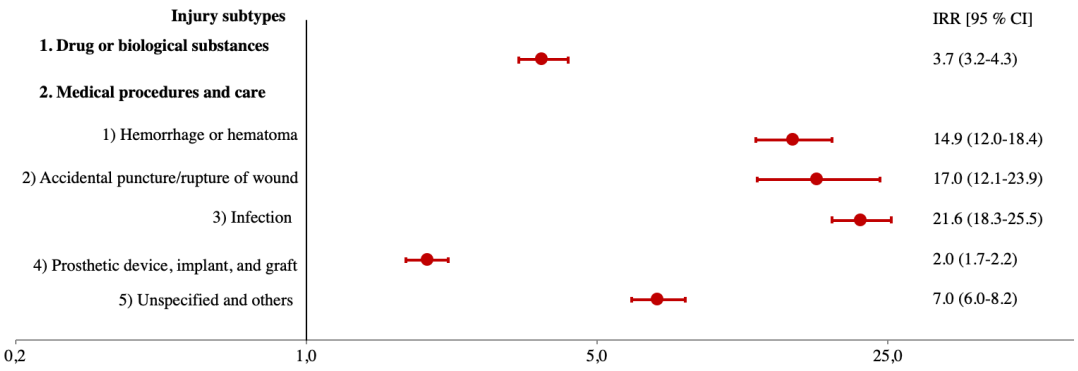


Figure 6.1.3 Incidence rate ratios and 95% CI of iatrogenic injuries during the diagnostic period compared to the pre-diagnostic period by injury subtypes, among 720,901 cancer patients diagnosed during 1991-2009 in Sweden.

X-axis was displayed on logarithmic scale of base 10 for better visualization.

Non-iatrogenic injuries

We identified in total 8,331 non-iatrogenic injuries among all cancer patients during the diagnostic period, representing an IR of 0.69 per 1,000 person-months. Compared to the pre-diagnostic period, we found an increased rate of non-iatrogenic injuries throughout the diagnostic (IRR, 1.9; 95% CI, 1.8 to 2.0) and post-diagnostic (IRR 2.0; 95% CI 1.9 to 2.1) periods (Figure 6.1.4). The rate increase was similar during diagnostic period and post-diagnostic period for all cancers, with some variations across cancer subgroups. During the diagnostic period, the highest rate increase was observed for patients with lymphatic or hematopoietic cancers and cancers of central nervous system.

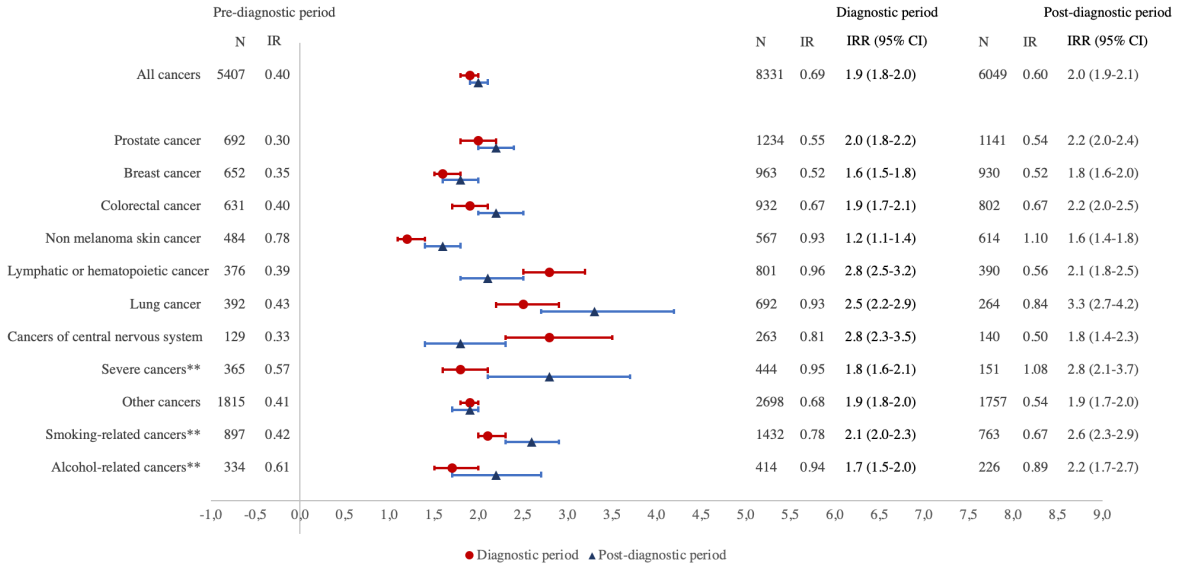


Figure 6.1.4 IRs (per 1,000 person-months) and IRRs of non-iatrogenic injuries during the diagnostic period and post-diagnostic period, compared to the pre-diagnostic period, among 720,901 cancer patients diagnosed during 1991-2009 in Sweden*

** Severe cancers include cancers of esophagus, liver, and pancreas. Smoking-related cancers include cancers of mouth, nasopharynx, esophagus, pancreas, lung, kidney, bladder and urinary track. Alcohol-related cancers include cancers of mouth, larynx, esophagus, biliary duct and liver.

When focusing on smaller time intervals during diagnostic period, the rate of non-iatrogenic injuries was noted to increase largely from four weeks before to two weeks after cancer diagnosis, with highest rate increase observed during the two weeks before cancer diagnosis (IRR 5.3; 95% CI, 4.6 to 6.1) (Figure 6.1.2). The rate increment was declined after two weeks post cancer diagnosis. Similar to iatrogenic injuries, the rate increase during post-diagnostic period for non-iatrogenic injuries constantly decreased over time. We observed an increased rate of non-iatrogenic injuries during diagnostic period compared to the pre-diagnostic period for most injury subtypes, except for injuries occurred in sports and athletics area and assault (Figure 6.1.5).

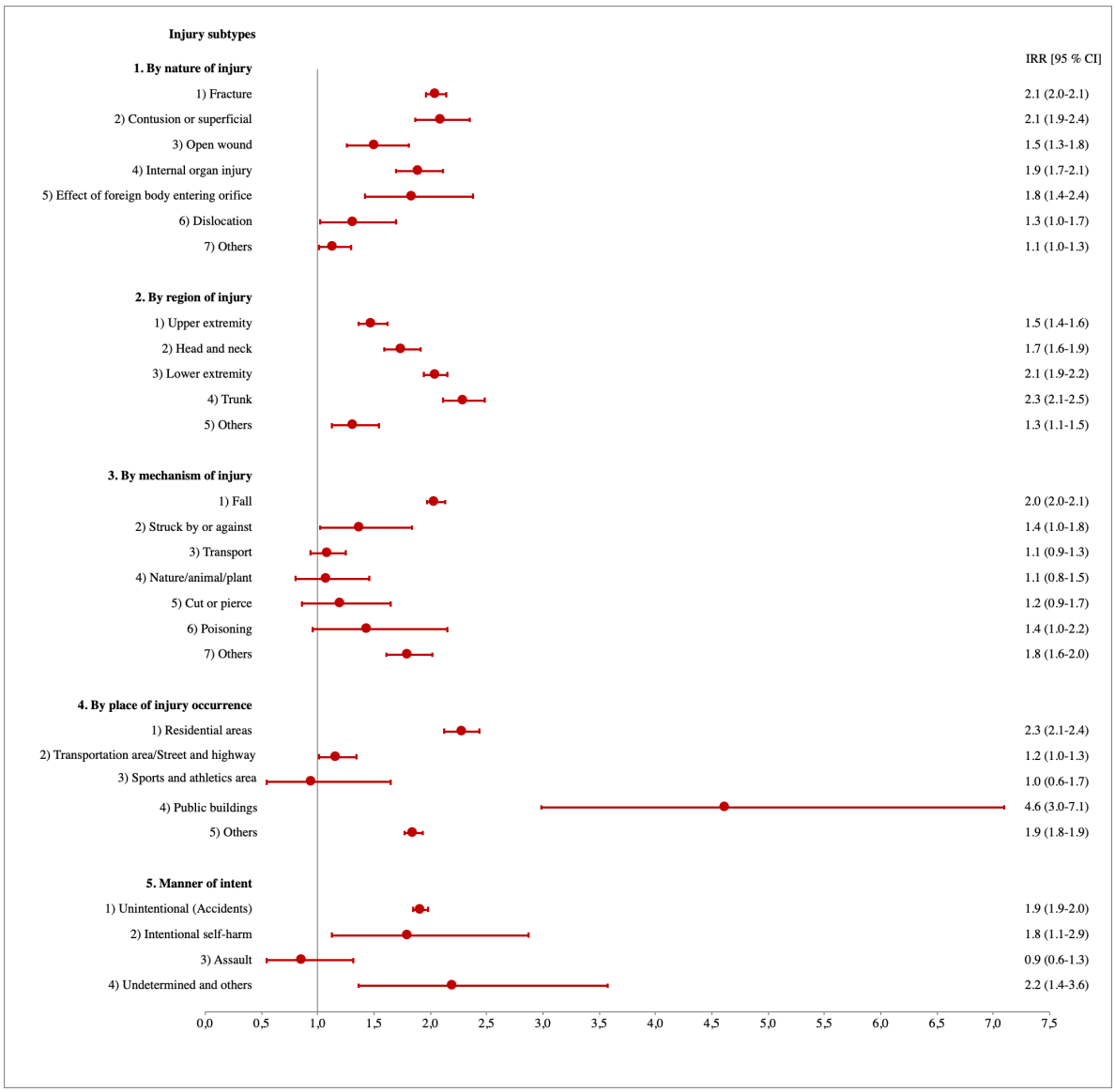
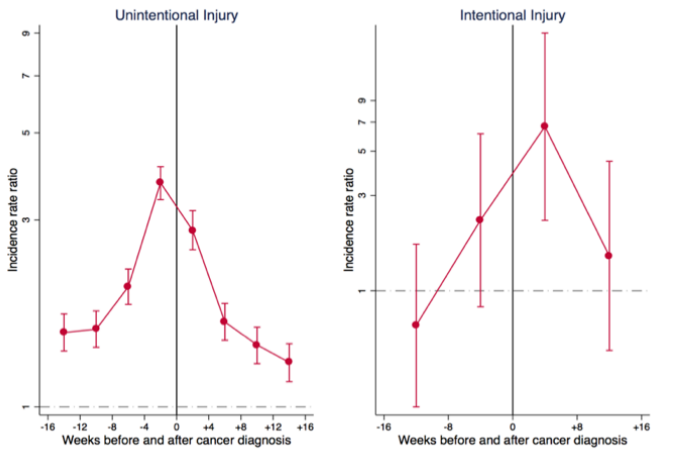


Figure 6.1.5 IRRs and 95% CI of non-iatrogenic injuries during the diagnostic period compared to the pre-diagnostic period by injury subtypes, among 720,901 cancer patients diagnosed during 1991-2009 in Sweden.

When focusing on the most common types of non-iatrogenic injuries by manner of intent, there was an increased rate of unintentional and intentional injuries before and after cancer diagnosis (Figure 6.1.6). An increased rate of unintentional injuries was noted from four weeks before to four weeks after cancer diagnosis. The increased rate of intentional injuries, i.e. self-harm behaviors, was observed only



during the weeks after cancer diagnosis.

Figure 6.1.6 IRRs and 95% CI of non-iatrogenic injuries during the diagnostic period compared to the pre-diagnostic period by unintentional and intentional injury, among 720,901 cancer patients diagnosed during 1991-2009 in Sweden.

*Time is divided into every four weeks for unintentional injuries and every eight weeks for intentional injuries, due to smaller numbers of the latter.

6.2 INJURIES IN RELATION TO DIAGNOSTIC WORKUP OF CERVICAL CANCER (STUDY II)

There were 1,853,510 women with only normal smear result, representing 95.6% of all participants. When characterizing women by histology diagnosis, 22,435 women with CIN1, 20,692 women with CIN2 and 36,542 women with CIN3/AIS were identified during follow-up. The number of women with invasive cervical cancer was 5,189 (0.3% of all participants). About half of the diagnostic workups of women with invasive cervical cancer started from a cytological smear (52.5%). Approximately 76% of the exposed women underwent a surgical treatment, including 44% of women with CIN1, 75% of women with CIN2, 80% of women with CIN3/AIS, and 49% of women with invasive cancer. Advanced histology diagnosis was associated with older age at diagnosis, earlier calendar period, lower screening adherence, lower education level, lower income, and non-cohabitation status (Table 6.2.1).

Table 6.2.1. Characteristics of study participants by histology diagnosis, a nationwide cohort study during 2001-2012 in Sweden.

Characteristics	Normal smear	CIN1*	CIN2*	CIN3/AIS*	Invasive cervical cancer	P value
No. (%)	1 853 510 (95.62)	22 435 (1.16)	20 692 (1.07)	36 542 (1.89)	5 189 (0.27)	
Workup started from cytological smear (%)						
Yes	100	99.96	97.81	95.65	52.51	
No	-	3.17	2.19	4.35	47.49	
Age, years (%)						<.0001
18-40	53.63	70.35	77.32	76.31	24.11	
41-65	45.74	27.77	21.39	22.17	36.85	
>65	0.63	1.88	1.29	1.52	39.04	
Calendar period (%)						<.0001
2001-2004	70.46	29.98	31.32	34.01	36.15	
2005-2008	17.69	29.14	30.35	32.93	32.36	
2009-2012	11.86	40.88	38.33	33.06	31.49	
Screening adherence (%)						<.0001
Low	35.11	22.38	21.97	43.02	68.82	
Medium	22.12	18.22	17.47	15.43	10.85	
High	23.10	22.61	22.38	13.57	10.10	
Very high	19.67	36.80	38.18	27.98	10.23	
Education (%)						<.0001
<9 years or unknown	11.62	9.00	9.83	11.10	34.09	
9-12 years	49.13	48.60	50.01	51.46	42.69	
>12 years	39.26	42.40	40.15	37.44	23.22	
Income (%)						<.0001

Low	27.74	23.51	25.33	28.08	28.70	
Medium	27.80	25.12	25.00	25.57	31.78	
High	26.71	26.51	26.16	24.66	21.60	
Very high	17.75	24.87	23.51	21.70	17.92	
Cohabitation status (%)						<.0001
Not cohabitating	58.55	79.71	81.84	76.01	66.33	
Cohabitating	41.45	20.29	18.16	23.99	33.67	

*CIN = Cervical intraepithelial neoplasia, CIN3/AIS includes carcinoma *in situ* and adenocarcinoma *in situ*.

Iatrogenic injuries with more than two days of hospital admission

There were 13 and 26 iatrogenic injuries identified between cytology and histology, and between histology and treatment among all exposed women, respectively (Table 6.2.2). Compared to women with normal smear, no statistically significantly increased rate of iatrogenic injuries was observed after cytology and before histology among women with LSIL and HSIL (IRR,1.93; 95% CI 0.99-3.78; IRR,1.25, 95% CI 0.39-4.07). Women with CIN3/AIS and invasive cancer had an increased rate after histology and before treatment (IRR,3.81, 95% CI 1.83-7.93 for CIN3/AIS; IRR,15.74, 95% CI 6.42-38.61 for invasive cancer). All women exposed to a diagnostic workup had an increased rate of iatrogenic injuries during the post-workup period, with much greater magnitude of rate increase compared to that of the diagnostic workup, especially for women with invasive cancer. Similar results were noted when considering only the first iatrogenic injury event per woman.

Table 6.2.2 Incidence rates (IRs, per 1 000 person-months) and incidence rate ratios (IRRs) of iatrogenic injuries during the diagnostic workup of women with cervical cancer and its precursor lesions, compared to women with normal smear, a nationwide cohort study during 2001-2012 in Sweden

	No. of women	No. of events	Crude IRs	IRR (95% CI)
Iatrogenic injuries that required ≥2 days of hospital admission				
Normal smear†	1 853 510	103	0.03	1.0
Between cytology and histology‡				
LSIL	44 519	10	0.05	1.93 (0.99-3.78)
HSIL	31 591	3	0.04	1.25 (0.39-4.07)
Between histology and treatment‡				
CIN1	22 435	5	0.04	1.51 (0.59-3.87)
CIN2	20 692	4	0.04	1.73 (0.62-4.81)
CIN3/AIS§	36 542	9	0.11	3.81 (1.83-7.93)
Invasive cancer	5 189	8	1.07	15.74 (6.42-38.61)
Post-workup period ‡				
CIN1	22 435	16	0.13	4.55 (2.58-8.03)
CIN2	20 692	24	0.21	7.41 (4.62-11.88)
CIN3/AIS§	36 542	88	0.42	13.50 (9.94-18.33)
Invasive cancer	5 189	44	2.07	41.01 (24.80-67.83)

† Normal smear: a 2-month period starting from the day of smear for women with normal smear.
‡ Between cytology and histology: between the first cytology and the first histology among women with both cytology and histology in the diagnostic workup. Between histology and treatment: between the first histology and treatment for women that were treated surgically and between the first histology and two months after for women that were not treated surgically (including women without cytology). Post-workup period was defined as a 6-month period after diagnostic workup.
§ CIN3/AIS includes *in situ* and adenocarcinoma *in situ*.

Non-Iatrogenic injuries

We identified, in total, 37 and 51 non-iatrogenic injuries between cytology and histology, and between histology and treatment among all exposed women, respectively (Table 6.2.3). Compared to women with normal smear, we did not observe a statistically significant increased rate of non-iatrogenic injuries between cytology and histology among women with LSIL and HSIL (IRR,0.86, 95% CI 0.56-1.33; IRR,1.35, 95% CI 0.80-2.28). Between histology and treatment, there was an increased rate among women with invasive cervical cancer (IRR,3.86, 95% CI 1.99-7.51) but not for women with CIN1, CIN2, or CIN3/AIS. Among women with invasive cancer, the rate increase of non-iatrogenic injuries during diagnostic workup was compariable to the post-workup period after treatment (Table 6.2.3). Similar results were noted when only accounting the first injury event per woman.

Table 6.2.3 Incidence rates (IRs, per 1 000 person-months) and incidence rate ratios (IRRs) of non-iatrogenic injuries during the diagnostic workup of women with cervical cancer and its precursor lesions, compared to women with normal smear, a nationwide cohort study during 2001-2012 in Sweden*

	No. of women	No. of events	Crude IRs	IRR (95% CI)
Non-iatrogenic injuries that required at least one day of hospital admission				
Normal smear†	1 853 510	460	0.12	1.0
Between cytology and histology‡				
LSIL	44 519	22	0.12	0.86 (0.56-1.33)
HSIL	31 591	15	0.20	1.35 (0.80-2.28)
Between histology and treatment‡				
CIN1	22 435	18	0.14	0.97 (0.52-1.84)
CIN2	20 692	11	0.12	0.88 (0.48-1.60)
CIN3/AIS§	36 542	13	0.16	1.08 (0.59-1.95)
Invasive cancer	5 189	9	1.20	3.86 (1.99-7.51)
Post-workup period ‡				
CIN1	22 435	18	0.15	1.07 (0.66-1.74)
CIN2	20 692	15	0.13	0.97 (0.55-1.71)
CIN3/AIS§	36 542	28	0.13	0.89 (0.60-1.33)
Invasive cancer	5 189	24	1.13	3.80 (2.45-5.90)

† Normal smear: a 2-month period starting from the day of smear for women with normal smear.
‡ Between cytology and histology: between the first cytology and the first histology among women with both cytology and histology in the diagnostic workup. Between histology and treatment: between the first histology and treatment for women that were treated surgically and between the first histology and two months after for women that were not treated surgically (including women without cytology). Post-workup period was defined as a 6-month period after diagnostic workup.
§ CIN3/AIS includes *in situ* and adenocarcinoma *in situ*.

6.3 PSYCHIATRIC DISORDERS AND CARDIOVASCULAR DISEASES DURING DIAGNOSTIC WORKUP OF BREAST CANCER (STUDY III)

During the study period, 15, 714 women with lump in breast were diagnosed, with a mean age of 41 years. The age at diagnosis for 4,435 women with benign tumor and 8,512 women with breast cancer were 45 and 63 years. Among women with breast cancer, 90% were treated surgically. The proportion of women receiving surgical treatment were 30% for patients with benign tumor and less than 2% for patients with unspecified lump in breast. The proportion of

women with breast cancer that had pre-existing cardiovascular diseases was 37%, while the proportion was 19% for women with either lump in breast or benign tumor.

Psychiatric disorders

During the six weeks before diagnosis, we identified 521 women with unspecified lump in breast, 145 women with benign tumor, and 253 women with breast cancer that had psychiatric disorders, corresponding to 3.3%, 3.3%, and 3.0% of all women with lump, benign tumor and breast cancer, respectively.

There was an increased rate of psychiatric disorders among all women exposed to a breast diagnostic workup, compared to the reference group (IR, 25.5 per 1,000 person-months; IRR, 1.2; 95% CI, 1.1-1.3). We found a marginally increased rate among women with unspecified lump in breast (IRR, 1.1; 95% CI, 1.0 to 1.2), and a statistically significantly increased rate among women with benign tumor (IRR, 1.3; 95% CI, 1.1 to 1.5) and breast cancer (IRR, 1.4; 95% CI, 1.2 to 1.6) (Figure 6.3.1). The rate increase was greater for breast cancer patients with advanced stage, compared to those with a lower stage. A rate increase was noted for anxiety before diagnosis of unspecified lump in breast, for stress reaction or adjustment disorder and substance abuse before diagnosis of benign tumor and for all individual psychiatric disorders before diagnosis of breast cancer. Similar rate increase of psychiatric disorders was noted during the six weeks before diagnosis for women that had a breast diagnostic workup due to symptoms, but not due to screening (Figure 6.3.2).

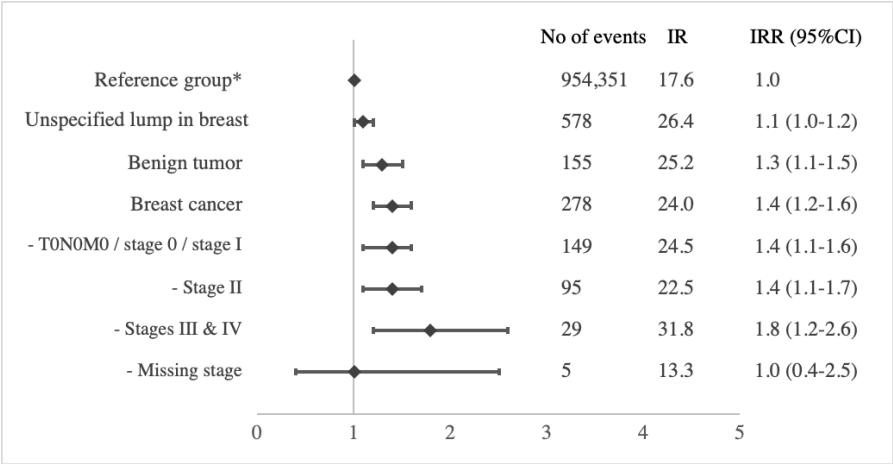


Figure 6.3.1. IRs (per 1000 person-months) and IRRs of psychiatric disorders during the six weeks before diagnosis of women that underwent a breast diagnostic workup, a population-based cohort study during 2005-2014 in Skåne, Sweden.

*Reference group included person-time accumulated from women who did not have any breast diagnostic workup during the follow-up and the person-time accumulated before the start of workup from women with a breast diagnostic workup during the follow-up.

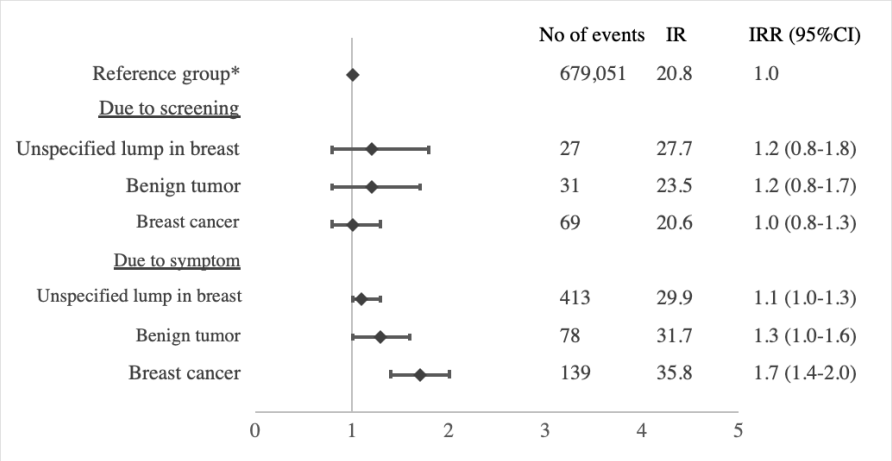


Figure 6.3.2. IRs (per 1000 person-months) and IRRs of psychiatric disorders during the six weeks before diagnosis, among women that had a breast diagnostic workup during 2009-2014 in Skåne, Sweden, analysis according to reason for diagnostic workup.

*Reference group included person-time accumulated from women who did not have any breast diagnostic workup during the follow-up and the person-time accumulated before the start of workup from women with a breast diagnostic workup during the follow-up.

Cardiovascular diseases

During the six weeks before diagnosis, 1.8% (N=284) of women with unspecific lump in breast, 2.5% (N=110) of women with benign tumor, and 8.3% (N=708) of women with breast cancer had a diagnosis of cardiovascular diseases. Among all exposed women, there was an increased rate of cardiovascular diseases during the six weeks before diagnosis (IR, 30.0 per 1000 person-months; IRR, 1.5; 95% CI, 1.5 to 1.6). The rate increased was observed mainly among women with benign tumor (IRR, 1.3; 95% CI, 1.1 to 1.6) and breast cancer (IRR, 1.9; 95% CI, 1.8 to 2.0). The rate increase was minimal among women with unspecified lump in breast (IRR, 1.1; 95% CI, 1.0 to 1.2) (Figure 6.3.3). The rate increase was greater for advanced breast cancer compared to a lower stage cancer.

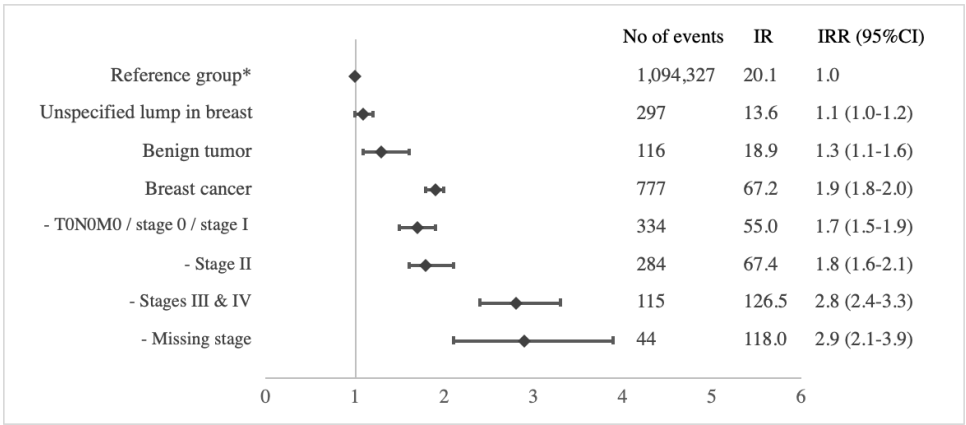


Figure 6.3.3. IRs (per 1000 person-months) and IRRs of cardiovascular diseases during the six weeks before diagnosis of women that underwent a breast diagnostic workup, a population-based cohort study during 2005-2014 in Skåne, Sweden.

*Reference group included person-time accumulated from women who did not have any breast diagnostic workup during the follow-up and the person-time accumulated before the start of workup from women with a breast diagnostic workup during the follow-up.

There was an increased rate for other diseases of the circulation system before the diagnosis of unspecified lump in breast, and for hypertensive diseases or aneurysm of the heart before the diagnosis of benign tumor. We found a higher rate for most types of cardiovascular diseases before the diagnosis of breast cancer. We found a rate increase of cardiovascular diseases during the six weeks before diagnosis for women that had a breast diagnostic workup due to screening and women that had a diagnostic workup due to symptoms (Figure 6.3.4).

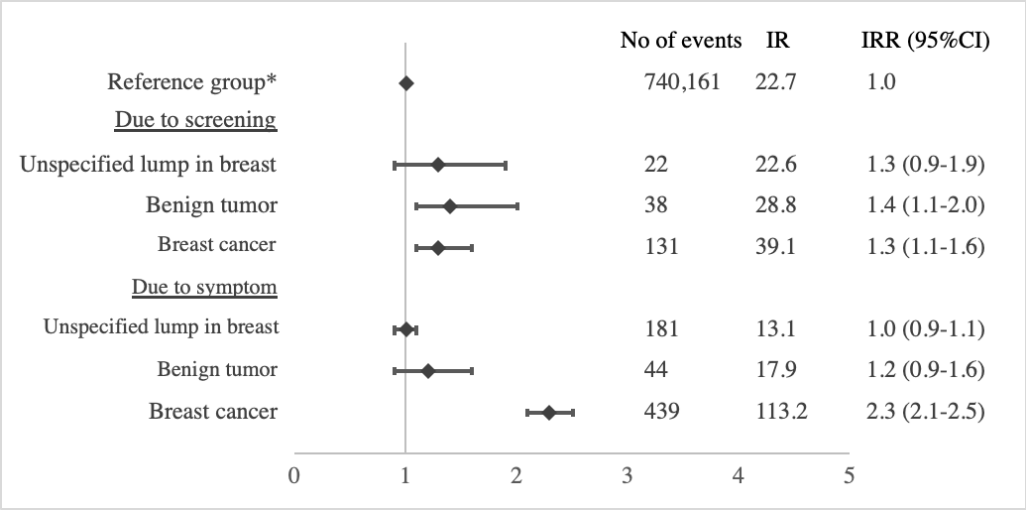


Figure 6.3.4 IRs (per 1000 person-months) and IRRs of cardiovascular diseases during the six weeks before diagnosis, among women that had a breast diagnostic workup during 2009-2014 in Skåne, Sweden, analysis according to reason for diagnostic workup.

*Reference group included person-time accumulated from women who did not have any breast diagnostic workup during the follow-up and the person-time accumulated before the start of workup from women with a breast diagnostic workup during the follow-up.

6.4 NSAID USE AND UNNATURAL DEATHS AFTER CANCER DIAGNOSIS (STUDY IV)

Among all cancer patients, 29.7% of the cancer patients used aspirin (N=115,320) and 29.1% used non-aspirin NSAIDs (N=112,994) during follow-up. The mean age at diagnosis was 74 years for patients with aspirin use, and 65 years for patients without aspirin use. The mean age was 64 years for patients with use of non-aspirin NSAIDs, and 69 years for patients without use of non-aspirin NSAIDs. Compared to patients without aspirin use, patients with aspirin use were more likely to be male, older at cancer diagnosis, less educated, unemployed or retired, and had higher chronic disease score. Patients with non-aspirin NSAID use were younger, more educated, more likely to be cohabitating, and have lower chronic disease score, compared to patients without use of non-aspirin NSAIDs.

Completed suicide

There were 287 completed suicides observed during follow-up, among which, 59 were during the on-medication period of aspirin and 13 were during the on-medication period of non-aspirin NSAIDs (Table 6.4.1). We did not observe a statistically significant association between use of aspirin (HR 0.96, 95% CI 0.66-1.39) or non-aspirin NSAIDs (HR 0.95, 95% CI 0.42-2.18) and the risk of completed suicide after cancer diagnosis.

Table 6.4.1. Association of NSAID use with risk of death due to suicide or accident after cancer diagnosis; a cohort study of 388,443 cancer patients diagnosed between Oct 2005 and Dec 2014 in Sweden

Characteristics	Completed suicide		Death due to accident	
	N	HR (95% CI)*	N	HR (95% CI)*
Low-dose aspirin use				
Off medication (Ref)¶	228	1.0	1 627	1.0
On medication	59	0.96 (0.66-1.39)	651	0.78 (0.70-0.87)
Use of non-aspirin NSAIDs				
Off medication (Ref)¶	274	1.0	2 219	1.0
On medication	13	0.95 (0.42-2.18)	59	0.92 (0.68-1.26)

*HR, hazard ratio; CI, confidence interval; analyses were adjusted for sex, age at diagnosis, cancer grade, cancer type, highest education level, occupation, cohabitation status, history of psychiatric disorders, chronic disease score, and calendar year of cancer diagnosis; time since cancer diagnosis was used as the underlying timescale.
¶Off medication time included follow-up time accumulated among patients without any dispensed NSAIDs during follow-up, as well as the non-medicated periods from patients that had any dispensed NSAIDs.

Death due to accident

There were in total 2,278 deaths due to accident during follow-up, among which, 651 were during on-medication period of aspirin and 59 were during the on-medication period of non-aspirin NSAIDs (Table 6.4.1). Aspirin use was associated with a 22% lower risk of death due to accident (HR, 0.78; 95% CI, 0.70-0.87). No association was however noted for non-aspirin NSAIDs (HR, 0.92; 95% CI, 0.68-1.26). The PAF analysis suggested that 16% (9-22%) of the deaths due to accident could have been avoided if patients had used aspirin during off-medication period. We found that the reduction in the risks of different types of accidents were similar, when separately estimating the association between aspirin use and different types of death due to accident (Figure 6.4.1).

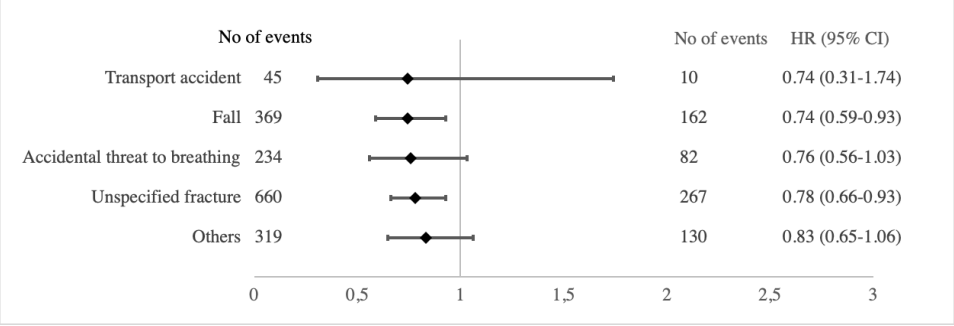


Figure 6.4.1. Association of aspirin use with the risk of death due to different types of accidents, a cohort study of 388,443 cancer patients diagnosed between Oct 2005 and Dec 2014 in Sweden

The risk reduction was more prominent among patients who were men, with a cancer diagnosed at early age (<60), with hematopoietic malignancies, without a history of psychiatric disorders, or with higher chronic disease score (Figure 6.4.2).

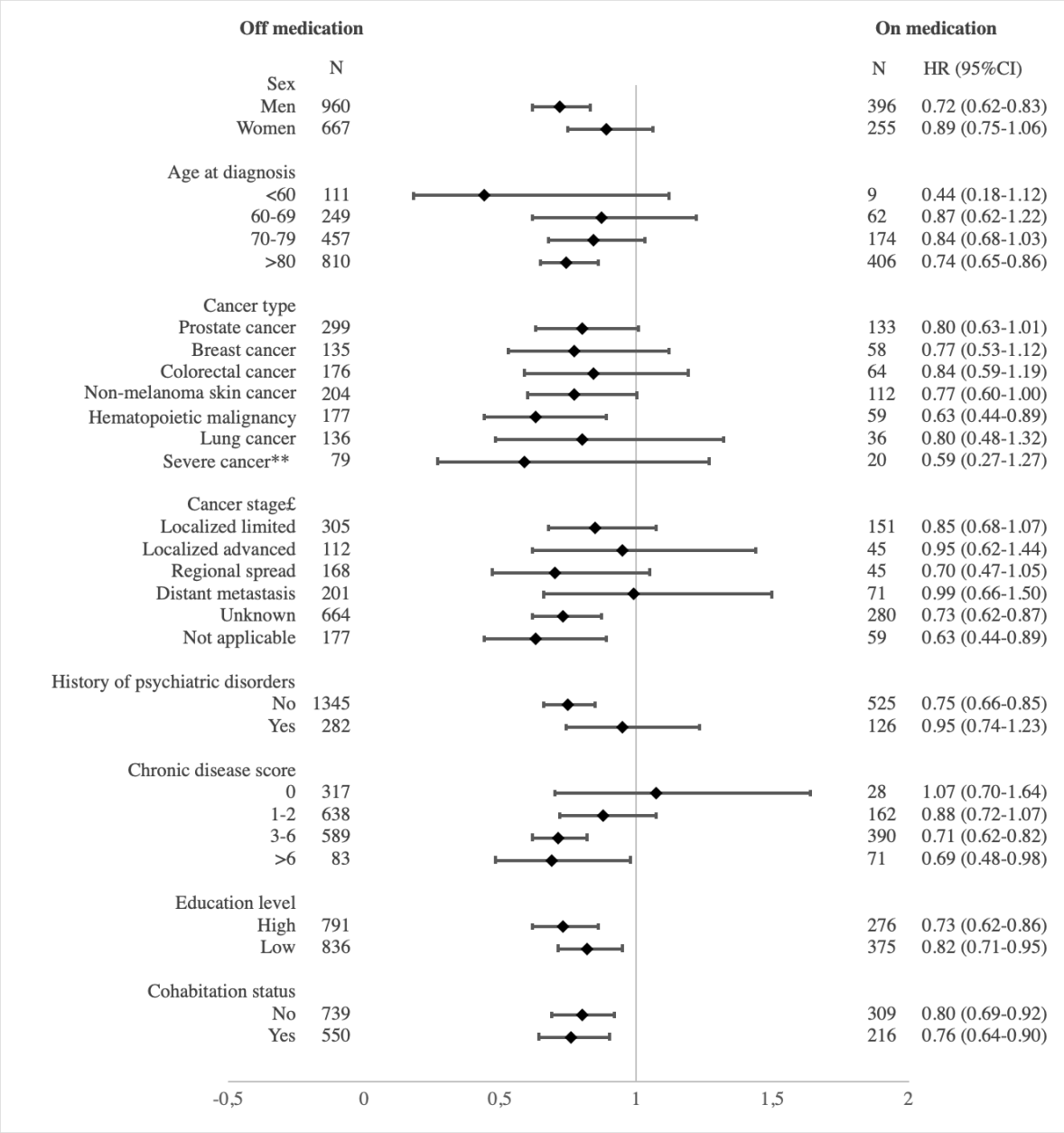


Figure 6.4.2. Association of NSAID use with risk of death due to accident after cancer diagnosis by patient characteristics; a cohort study of 388,443 cancer patients diagnosed between Oct 2005 and Dec 2014 in Sweden

*HR, hazard ratio; CI, confidence interval; analyses were adjusted for sex, age at diagnosis, cancer grade, cancer type, highest education level, occupation, cohabitation status, history of psychiatric disorder, chronic disease score, and calendar year of cancer diagnosis; time since cancer diagnosis was used as the underlying timescale.
¶Off medication time included follow-up time accumulated among patients without any dispensed NSAIDs during follow-up, as well as the non-medicated periods from patients that had any dispensed NSAIDs.
£Defined by European Network of Cancer Registries Condensed TNM Scheme and International Federation of Gynecology and Obstetrics staging system: localized limited (T-localized/N0/M0 or FIGO 0-I), localized advanced (T-advanced/N0/M0 or FIGO II), regional spread (any T/N+/M0 or FIGO III), distant metastasis (any T/any N/M+ or FIGO IV), or unknown stage. Hematological malignancies were classified as not applicable.
**Severe cancer included cancers of esophagus, liver and pancreas.

7 DISCUSSION

7.1 FINDINGS AND IMPLICATIONS

7.1.1 Stress-related health outcomes during cancer diagnostic workup (Study I, II, III)

Injury is one of the leading causes of non-cancer deaths among cancer patients (1). Existing studies have mostly focused on the risk of fatal outcomes, after cancer diagnosis or treatment, or during the later phase of cancer survivorship. Little is however known about the risks of non-fatal severe injuries during the diagnostic process of cancer. Study I represents the first systematic investigation of non-fatal iatrogenic and non-iatrogenic injuries immediately before and after a cancer diagnosis. We found that cancer patients had an increased rate of iatrogenic injuries starting from two weeks before diagnosis, and an increased rate of non-iatrogenic injuries from four weeks before diagnosis. The rise in the rate decreased over time during the period after diagnosis, after a peak around diagnosis. In contrast to a smaller and decreasing risk in magnitude over time during post-diagnostic period, these findings demonstrate therefore a significant impact of cancer diagnostic process and subsequent treatment on risk of hospitalized injuries.

Non-iatrogenic injuries

An increased risk of self-injury and accidental death during the first year after cancer diagnosis has been reported among cancer patients in Sweden (22), the United States (54), and Japan (47). In our study, we further noted that the rate of hospitalized non-iatrogenic injuries started to increase already from four weeks before cancer diagnosis. This finding is consistent with previous studies demonstrating a high level of psychological distress when patients were awaiting for a cancer diagnosis (21,28). The rate increase during diagnostic period was noted for both intentional and unintentional injuries, with unintentional injuries to be a more common outcome. It is important to note that the increased rate of unintentional injuries was observed both before and after cancer diagnosis, whereas only after cancer diagnosis for intentional injuries. This is in line with previous findings showing a significant risk increase of suicide immediately after receiving a cancer diagnosis (22,40,49). These results may indicate different mechanisms underlying the rate increase of these injuries before and after diagnosis. In addition to symptoms of a progressing disease, the increased rate of non-iatrogenic injuries before cancer diagnosis, mainly unintentional injuries, might be attributed to the cognitive impact of an upcoming cancer diagnosis, including impaired attention and concentration. Besides the cognitive impact, stress-related psychiatric symptoms, such as depression and suicidal ideation, might as well contribute to the rate increase after diagnosis.

The rate increase of non-iatrogenic injuries was observed among all cancers and the magnitude varied across cancer types, with the smallest rate increase noted among patients with non-melanoma skin cancer, a cancer type with relatively mild symptoms and benign prognosis. Older patients, patients with non-cohabitation status, and patients with lower socioeconomic

status and education level were at higher rate of non-iatrogenic injuries, indicating that these groups of patients were more vulnerable to such health outcomes when facing a stressful life event. Incidence rate of non-iatrogenic injuries was higher among patients with pre-existing psychiatric disorders or previous history of injury, while greater relative risk was noted among patients without such histories.

It has been noted that the social stigma related to cervical cancer might further contribute to a high level of psychological distress (79). Women receiving an abnormal test result when evaluated for cervical cancer had indeed been reported to have increased risk of anxiety, distress, sleep disturbance, and poor concentration (80–82,162,163). In Study II, we found an increased rate of non-iatrogenic injuries during the diagnostic workup and the post-workup period of women with cervical cancer, although the number of injuries was small during both time periods. During the diagnostic workup, the rate increase was noted after biopsy, i.e. when waiting for a diagnosis. We did not find a clear rate increase of non-iatrogenic injuries among women with cervical precursor lesions. This might be explained by a lower degree of psychological distress in relation to receiving a benign diagnosis with a higher possibility to be cured (76). We need to note that the inpatient care of non-iatrogenic injuries was very rare during the diagnostic workup of cervical cancer and precursor lesions, denoting a minimal public health impact from such health outcome.

Psychiatric disorders and cardiovascular diseases

High level of psychological distress and its resultant health outcomes, including psychiatric disorders, are increasingly recognized among breast cancer patients (33,164). Patients with breast cancer and breast cancer *in situ* were shown to have an increased risk of depression, anxiety and stress-related disorders after diagnosis (109). Previous studies have also found that women with breast cancer were more likely to die from cardiovascular events (114), both during the immediate time period after receiving a cancer diagnosis (22) and after treatment (165,166). Evidence is however limited on the risk of cardiovascular and psychiatric comorbidities before receiving a breast cancer diagnosis, where the psychological distress might be equally, if not more, significant (23). In Study III, we conducted an assessment of the risk of psychiatric disorders and cardiovascular diseases during the time period immediately before diagnosis and found an increased rate of clinically diagnosed psychiatric disorders and cardiovascular diseases. The rate increase was noted for women diagnosed with benign tumor in breast and breast cancer. The rate increase was minimal among women diagnosed with unspecified lump in breast. The results from self-comparison design confirmed the findings after adjusting for shared and unmeasured risk factors that were consistent over time. This finding demonstrates that the psychological stress in relation to being evaluated for a potential breast cancer is experienced not only by women with malignant and fatal diseases, i.e. cancer, but also by women with benign tumor. The rate increase was however not noted among women with unspecified lump in breast. In addition to psychological stress, the result pattern might also be explained by the role of tumor-related inflammation on the development of stress-related disorders (167,168). Women with a diagnostic workup of breast cancer due to

symptoms had a higher rate of both outcomes, compared to women with a workup due to screening. This finding might reflect the impact of disease characteristics. Cancer patients with symptoms at the time of diagnosis often have more advanced tumor stage compared to cancer patients that are detected upon screening (169). The psychological impact from breast cancer screening has since long been discussed and often suggested to be minimal or neglectable as compared to the screening benefits (104,108,111,170). Our findings suggests that the adverse health impact from cancer evaluation has likely been underestimated in previous studies using cancer screening programs alone, where patients with symptoms are often not included (170,171). We found a similar rate increase of psychiatric disorders and cardiovascular diseases during the weeks before diagnosis, compared to the rate increase between diagnosis and treatment (mostly surgery for cancer patients). This indicates a sustained and comparable high level of psychological stress when waiting for a cancer diagnosis and when waiting for a cancer treatment.

Psychiatric disorders and cardiovascular diseases might both represent a high level of perceived psychological stress in relation to breast cancer diagnostic workup. We combined both outcomes as one outcome, defined as having a diagnosis of either a psychiatric disorder or a cardiovascular disease. The results are largely similar to that when analysing these two outcomes separately. Patients with both outcomes during this critical time window might represent a particularly high-risk group. However, the proportion of women with both outcomes during the weeks before diagnosis was very small, including less than 1% of women among each group. We were therefore unable to further investigate these women.

7.1.2 Role of NSAID use on severe stress-related health outcomes after cancer diagnosis (Study IV)

Despite of evidence showing an increased risk of death due to accidents and suicide among cancer patients (22,47,54,172), the underlying reasons of such risk increase are not clearly understood. Inflammation can be a possible pathway between psychological stress related to receiving a cancer diagnosis and treatment, and its subsequent health outcomes. In Study IV, we assessed the potential effect of anti-inflammatory drug use in modulating the risk of severe stress-related health outcomes, using death due to suicide or accidents as examples. To the best of our knowledge, Study IV is the first study to investigate the effect of anti-inflammatory drug use on the risk of unnatural deaths among patients with a cancer diagnosis. We found that the use of low-dose aspirin was associated with a lower risk of unnatural death. We however did not observe an association between use of non-aspirin NSAIDs and unnatural death.

Aspirin is clinically used for prevention and treatment of cardiovascular and thromboembolic events (173). Aspirin has also been investigated for its potential use in reducing cancer-specific outcomes (139,174,175). Recently, aspirin use has been suggested to reduce the risk of stress-related health outcomes due to its anti-inflammatory properties (135,176). It is plausible that inflammation can drive changes in dopaminergic corticostriatal circuitry, which is correlated with deficits in motor function among distressed patients (131). The finding of reduced risk of death due to accidents might be explained by the anti-inflammatory properties of aspirin that

intervene in this process. This finding is also consistent with evidence from previous studies. Cognitive impairment and psychiatric disorders are known risk factors for suicide and injuries (177–180). Low-dose aspirin was found to prevent cognitive impairment in an animal model of breast cancer (181). In humans, cognitive impairment was associated with an increased risk of external injuries (132,133). Further, aspirin was shown to be associated with a decreased risk of depression and depressive symptoms and considered as a potential treatment for psychiatric disorders (134,135).

Although reduced risk of death due to accidents was clearly noted, we did not find a clear association between use of low-dose aspirin and risk of death due to suicide. It is possible that there was indeed no association between aspirin use and risk of suicide. It is also possible that a real association is concealed by the lack of statistical power due to very small number of suicide cases. When combining suicide and death due to accidents as one outcome (unnatural deaths), we found that use of low-dose aspirin was associated with a lower risk of unnatural deaths. Unlike death due to accidents, which is mostly unpredictable, completed suicide is intentional. During the immediate time period before suicide, patients might stop taking or dispensing medications due to a loss of interest in daily activities (182), leading to a distorted association.

Non-aspirin NSAIDs are commonly used as analgesics for arthritic pain, with analgesic, anti-inflammatory, and anti-pyretic therapeutic properties (183). This class of drugs is used in low dose and for short-term due to its side effect on gastrointestinal and cardiovascular systems (184–186). In our study, we did not observe an association between use of non-aspirin NSAIDs and the risk of death due to accidents or suicide. The contrasting results between use of low-dose aspirin and non-aspirin NSAIDs are not surprising. In a previous study, low-dose aspirin was found to be associated with a decreased risk of depression whereas non-aspirin NSAIDs were associated with an increased risk of depression (138). The possibility of chance finding cannot be excluded completely because of the relatively smaller number of outcomes noted during the on-medication period for other NSAIDs compared to aspirin.

7.1.3 Other health outcome – Iatrogenic injuries (Study I, II)

Although an increased mortality due to iatrogenic injuries was recognized for patients with colorectal cancer, prostate cancer, and breast cancer (114,187–189), data on burden of iatrogenic injuries among cancer patients is generally scarce. The increased risk of iatrogenic injuries during cancer diagnostic period, especially immediately after cancer diagnosis, is expected. Cancer patients undergo often invasive diagnostic procedures and treatments, and are as a result more likely to experience medical complications.

The burden of iatrogenic injuries is likely associated with the extensiveness of cancer treatment strategies (190). We found that patients with non-melanoma skin cancer had the lowest rate increase while patients with cancers of central nervous system and colorectal cancer had the greatest rate increase, of iatrogenic injuries. Patients with younger age, cohabitation status and higher socioeconomic status and education level had a higher increase in the rate of iatrogenic

injuries, reflecting the possible more aggressive treatments received by these groups. This is consistent with previous finding showing a declining use of definite cancer therapy among those with increasing age for cancer patients, independent of comorbidities (191). Patients with pre-existing psychiatric disorders or previous history of injury had a higher incidence rates, while patient without such histories had a higher relative risk, of iatrogenic injuries. Infection and bleeding were the most commonly identified iatrogenic injuries, compared to other subtypes.

Cervical cancer with a worse prognosis is often identified in women who abstain from cervical screening (192). One reason for women not participating in screening is the concern of safety in screening procedures (86), for instance, bleeding after punch biopsy (193). Although overnight watching for temporary discomfort might be expected after diagnostic procedures, to be hospitalized for a longer period of time is uncommon. Indeed, in our Study II, the number of iatrogenic injuries that required more than two days of inpatient care is very small during the diagnostic workup of women with cervical cancer and its precursor lesions. Compared to normal smear, we observed an increased rate of iatrogenic injuries during the diagnostic workup of cervical abnormalities, and such rate increase was greater after biopsy than after smear. This is expected because punch biopsy might cause bleeding and subsequently increase the risk of infection (86). Indeed, hemorrhage or hematoma and infections are the most common subtypes of iatrogenic injuries during the diagnostic workup of women with invasive cancer. We found a higher rate increase among women with invasive cancer than those with precursor lesions. Women with invasive cancer have commonly greater vascularity in tumor growth (194). Invasive cervical cancer is commonly diagnosed among women with older age and lower compliance to cervical cancer screening (76,192,195), which are both risk factors for surgery-related adverse events (62,63). The rise in the rate of iatrogenic injuries was smaller during the diagnostic workup compared to post-workup period. This finding indicates that the impact in relation to the diagnostic procedures is smaller than that of surgical treatment of cervical cancer and its precursors (196,197). It is however important to note that the inpatient care for two nights or more for iatrogenic injuries in relation to diagnostic workup of cervical abnormalities, either invasive cancer or its precursors, is extremely rare.

7.1.4 Significance

Our findings of increased rate of non-iatrogenic injuries from Study I call for prevention of self-harm and accidental injuries during the time of cancer diagnosis and primary treatment. Different prevention strategies should be designed to target different time periods and groups at high risk. In Study II, inpatient care of one night or longer for non-iatrogenic injuries was very rare during the diagnostic workup of invasive cervical cancer and precursor lesions, demonstrating the minimal public health impact during this time period for the cervical cancer screening population. There was however an increased risk of non-iatrogenic injuries during the diagnostic workup of women with invasive cervical cancer. Findings from Study I and II provide novel evidence for the magnitude of rise in the risk of stress-related injuries among patients with cancer in general as well as women with invasive cervical cancer. Although these

studies focused on injuries that require inpatient care, the findings of increased risk of such injuries before and after cancer diagnosis might also apply to milder injuries.

In Study III, the findings of increased rate of psychiatric disorders and cardiovascular diseases during weeks before diagnosis of breast cancer and benign breast tumor call for a better clinical surveillance of these two outcomes for women being evaluated for a potential breast cancer, regardless of the final diagnosis. The findings of higher rate increase of such outcomes during diagnostic workups due to symptoms compared to workups due to screening indicate that using screening population alone is not enough to comprehensively estimate the health impact of clinical breast cancer evaluation. The population exposed to a cancer diagnostic workup and its resultant adverse health impact is much larger than the population that eventually received a cancer diagnosis. In study III, only 30% of women received a diagnosis of breast cancer among all women who underwent a diagnostic workup of potential breast cancer.

Different prevention strategies should be designed to target different time periods before and after cancer diagnosis and in accordance to different procedures. High-risk groups as well as subtypes of stress-related health outcomes should be taken into account by the clinicians and policy makers to develop prevention strategies. For instance, patients who are in advanced age group, with advanced tumor stage, and without cohabitation status might be the potential high-risk groups. Specific outcomes including unintentional injuries (such as unspecified fall), stress reaction or adjustment disorder, depression and anxiety, and embolism or thrombosis are common outcomes, whereas intentional injuries such as suicidal behaviors are extreme outcomes. Both outcomes need to be specifically addressed.

Experiencing these health outcomes during the diagnostic workup may serve as a good proxy for vulnerabilities of potential cancer patients in coping with the evaluation process, including the diagnostic procedures, discomfort experience, potential side effects, perception of results, as well as subsequent treatment if needed. Such vulnerabilities may include a sub-optimal stress coping strategy, less resilient personality, lack of proper social support, lower socioeconomic standing, and risky behaviors. As a result, patients that already suffer from the diagnostic workup may also on average encounter more health problems later on. Knowledge obtained in these studies may add valuable evidence in guiding the healthcare system, the families and the society, in providing proper support to cancer patients already from the diagnostic workup of cancer. Improvement in management of cancer care, such as optimal waiting time and active surveillance during the diagnostic workup process might be implemented as a result.

The use of low-dose aspririn was found to be assocaited with a lower risk of unnatural death. This findings from Study IV provide valuable evidence for a potential effective approach to reduce the risk of severe stress-related health outcomes following a cancer diagnosis. Given the widely use of low-dose aspirin, the repurposing utility with the same dosage guarantees that the management of such treatment is safe and with low cost. Because it is often suggested to stop taking aspirin prior to major surgery in clinical practice, the results may also call for more studies in assessing the importance of aspirin reuptake after surgical treatment.

In addition to stress-related health outcomes, our findings also shed light on the burden of iatrogenic injuries around cancer diagnosis and call for attention to reduce such burden. Although it is hard to evaluate harms from benefits during intensive medical procedures of cancer care, the findings from Study I do provide evidence for a critical time window during the cancer evaluation and treatment process, in terms of potential prevention of iatrogenic injuries in cancer care. Study II adds evidence to the ongoing discussion about potential harms of cervical screening procedures. The occurrence of severe iatrogenic injuries during the cervical diagnostic procedures is extremely rare, showing the minimal health impact from such injuries to the screening population. Nevertheless, iatrogenic injuries still remain as public health concern for cancer patients at large. More attention is needed to better understand the burden and impact of such health outcomes in cancer care.

7.2 METHODOLOGICAL CONSIDERATIONS

Observational studies provide unique opportunity to search for evidence, in contrast to experimental studies, due to its longer time of follow-up, heterogeneous population, and real-world setting (198). Cohort study is the main study design used in this thesis. It represents a type of studies that follows a defined group of participants longitudinally to measure outcomes over time, under the impact of exposure of interest. Cohort study is considered to provide high rank of evidence in the pyramid of observational studies (199). It is feasible and effective to perform cohort study to assess common outcomes in favor of the prospectively collected information over a long period of time in well-established registers.

7.2.1 The comparison group

The comparison group, or reference group, is selected from those who are not exposed. Ideally, it is a group of people that is exactly the same as, or as similar as possible to, the exposed group except for exposure status, with respect to factors that could influence the studied association. Commonly, the comparison is performed between separate groups of individuals, known as between-individual comparison. Sometimes study participants can also be compared to themselves between different time periods, known as within-individual comparison.

In our studies, we used within-individual comparison, solely or in compensation to, between-individual comparison (in Study I and III). We compared each participant during different time periods of his or her self, to control for potential influence of shared or unmeasured confounders that remained fixed over time, such as genetic and environmental effects. Age impact is however not possible to control for by this design. In a within-individual comparison, all participants are included in the calculation of absolute risk while only those with different outcome status across comparison periods are included in the calculation of relative risk. This design has higher efficiency than using the entire cohort, with the consideration of decreasing sample size used for analysis of rare outcomes. Because it proxies a self-controlled case-series design, there are assumptions to rely on when applying this method (200). Firstly, outcomes should be independent recurrent events, or rare non-recurrent events. In Study I and III, recurrent outcomes within one week/one month of each other or with the same diagnostic codes

were not included in the outcome calculation. We also conducted a sensitivity analysis to only include the first outcome event during each time period, and the results confirmed largely the main findings. Secondly, when individuals experience multiple exposure periods, the occurrence of an event should not alter the probability of subsequent exposure (200). A common practice to avoid such bias is to exclude the pre-exposure time period leading to the subsequent exposure period from the reference period. In Study I, the design of this study automatically corrected for this possible bias by not using the time period immediately before the exposure period as the reference. In Study III, it might be possible that patients with frequent contact to healthcare system were more likely be detected with a cancer. However, the results obtained from this design were consistent with the main findings using a different design, largely alleviating the concern. Thirdly, the occurrence of event should not alter the observation period (200). The violation of this assumption can happen if an event of interest increases the death rate. In Study I, because fatal outcomes were not possible during pre-diagnostic period by design, we excluded patients that had fatal injuries during diagnostic period. Patients who could not survive until the start of post-diagnostic period did not contribute to the comparison between post-diagnostic period and pre-diagnostic period. In Study III, death during reference period that preceded exposure period was not possible by design. Previous studies have been carried out and showed the impact of such bias to be negligible (201,202).

7.2.2 Survival analysis and models

Survival analysis was conducted to measure time-to-event outcomes. The use of statistical analysis is affected by choice of study design. In cohort study, Poisson and Cox regression models can both estimate the relative risk in relation to the exposure. In Study I, II and III, we used Poisson regression models to allow for the repeated measurement of outcomes during follow-up. The outcomes of interest were hospitalized injuries that could happen repeatedly in Study I and II, and recurrent health visits due to psychiatric disorders and cardiovascular diseases in Study III. Conditional Poisson regression model was used after stratifying by the matched clusters in within-individual comparison in Study I and III (156). In Study IV, we used Cox regression model, also known as proportional hazards regression model, to investigate the constant effect of NSAID use on unnatural deaths after cancer diagnosis. Assumption of proportional hazards was tested using Schoenfeld residuals and no major violation of such assumption was found.

7.2.3 Bias and confounding

Our studies benefited from the minimized potential biases in the large-scale register-based studies with information collected on an entire population prospectively and independently. Despite of the high quality of information from registers, some biases still need to be discussed considering their potential impact on result interpretation.

Selection bias

Selection bias can be introduced if the study sample is not representative of the population intend to be enrolled in analysis. In cohort study, selection bias is induced when included

participants in the beginning of follow-up are not representative of the study population, or individuals who are lost to follow-up or withdraw from the study are different from those who remain in the follow-up. In our studies, we used Swedish population and health registers to follow the entire population living in Sweden or Skåne region, which has largely eliminated the potential selection bias. Of note, Study II enrolled all women that participated in organized or opportunistic screening. Non-response to cervical cancer screening programme might lead to selection bias to some extent if a selected group did not participate in cancer screening, for instance, women with low socioeconomic status. The coverage of cervical cancer screening was however 82% in 2016 across the country (148). In Study II, the estimates were barely changed after adjusting for education and income. We therefore speculate that the impact from socioeconomic status is minimal on the results of Study II. In all studies, emigration was regarded as one censoring outcome. Because emigration represents a small proportion of censoring and is not evidently to be associated with the studied outcomes, it is unlikely that loss due to emigration would have introduced selection bias to a large extent.

Information bias

Information bias, also called observational bias or misclassification, should be considered when the measurement of exposure, outcome or confounders is not always accurate. In general, the extent of information bias in this thesis is likely small, considering the fact that all information on exposure, outcome and key variables is required from population-based regional or national registers, instead of, for example, from self-reported information, although the information from registers is not always complete and correct.

Misclassification of exposure is less likely to occur in Study I, II and III, because of the almost complete coverage of newly diagnosed cancer from the Swedish Cancer Register, NKCx and SHR. Of note, date of diagnosis recorded in the Swedish Cancer Register represents by definition the date when the cancer diagnosis is determined clinically or through morphological examinations (18), not necessary when a patient is informed of the diagnosis. This recorded date in the register shall in most cases precede the date when patients are informed about the diagnosis. Another source of potential misclassification of exposure might be suspected in Study III, where women could be diagnosed with unspecified lump in breast before receiving a cancer diagnosis. Because time period before start of workup was counted to the reference group, it is possible that women with a breast cancer had previously been diagnosed with a lump and were misclassified as unexposed group before the workup for breast cancer. This might lead to a diluted association. In Study IV, the use of prescription text to quantify days on medication has largely eliminated the concern of misclassification of on- and off-medication periods. We however had no information from the register upon whether the patients in fact used the dispensed medications. This might result in an underestimation of the studied association as well. We conducted a sensitivity analysis to validate the definition for on- and off-medication period, by defining the first month after each on-medication period also as on-medication period rather than off-medication period. We found no difference of the associations.

Surveillance bias, also called detection bias, may occur when some groups are followed up more closely than others, leading to a more frequent outcome reporting among those who have been monitored closely. In Study I and II, we chose to use injuries attended at inpatient care as the main outcome of interest since inpatient visits was less prone to surveillance bias. In Study III, we had the unique opportunity to use all levels of healthcare provided in Skåne region. The inclusion of primary care visits might introduce potential surveillance bias because women who were exposed to a cancer diagnostic workup were more likely to be diagnosed with other health problems, than women who were not exposed. It is possible that some of the observed associations were due to surveillance bias. However, the rate increase of cardiovascular diseases observed from specialist care visits, in addition to primary care visits, during the diagnostic workup of potential breast cancer, rejected the claim that surveillance bias explained completely the findings. It might also be noted that such bias can be introduced by using repeated outcome measurements in Study I, II and III. To assess such impact, we included the first outcome during each time period as the outcome definition in a sensitivity analysis of these studies, and the results confirmed largely the main findings.

In Study IV, suicide is claimed to be a challenge in classifying causes of death, and can be misclassified as accidents (203). The misclassification of the suicidal outcome might have contributed to a lack of power to detect the true associations.

Confounding

The association between exposure and outcome can be distorted by confounding factors. By design, a within-individual comparison was used in Study I and III, which alleviated largely the concern of confounding factors that are fixed over time. In all analyses, we controlled for a couple of variables, including age, sex, calendar period, cohabitation status, socioeconomic status and history of preexisting diseases, which also eliminated the concern of confounding.

However, residual confounding cannot be excluded. For instance, in Study III, the use of registered parish as proxy for socioeconomic status might induce residual confounding. We cannot completely roll out the impact from other factors, such as use of psychiatric medications, behaviour and other social support. In Study II, information on tumour stage was not available during the study period, and the potential contribution of cancer stage on the risk of injures among women with cervical cancer was not addressed. In Study III, we had little clinical information, including detailed reasons of workup initiation, type of symptoms, and course of diagnostic workup, on women that underwent a diagnostic workup. Such detailed information was not available in register. In Study IV, confounding by indication or indication bias may occur when the observed association is related to indication for medication but not the use of medication. To alleviate this concern, we contrasted findings between aspirin and non-aspirin NSAIDs. The different result pattern between these two groups alleviated greatly the concern of confounding by indication assuming that it would have functioned in a similar direction for both drugs.

Generalizability

Many previous studies focused on highly selected participants, such as screened population from cancer screening programs, which is mostly likely to be well educated, higher in socioeconomic status, and healthier than the general population. Although our population-based studies are considered to have a good external validity in generalizing the findings to the entire Swedish population, our results shall be generalized with caution to other populations, especially to populations with different health care system and cancer screening protocols.

8 CONCLUSIONS

- We found that patients with a cancer diagnosis had an increased rate of iatrogenic and non-iatrogenic injuries attended by inpatient care, both before and after cancer diagnosis. The findings provide first evidence on the burden of medical complications and call for prevention of self-harm and accidental injuries during the critical time period of cancer diagnosis and treatment.

- The diagnostic procedures during cervical screening are safe in terms of severe iatrogenic and non-iatrogenic injuries. Although women with invasive cervical cancer had an increased rate of non-iatrogenic injuries in relation to receiving a diagnosis of cervical cancer, severe iatrogenic and non-iatrogenic injuries was very rare during the diagnostic workup of women with cervical cancer and its precursor lesions.

- Women evaluated for a suspected breast cancer had an increased rate of psychiatric disorders and cardiovascular diseases when waiting for the diagnosis. These rate increase appeared to be stronger for a diagnostic workup that was due to symptoms compared to a workup that was due to screening findings.

- We found that aspirin intake was associated with a lower risk of unnatural deaths after a cancer diagnosis. We did not find an association between use of non-aspirin NSAIDs and risk of unnatural deaths. Our study provides therefore evidence for a beneficial effect of low-dose aspirin use in reducing such severe health outcomes after a diagnosis of cancer.

9 FUTURE PERSPECTIVES

In Study I and II, we focused on injuries requiring inpatient care as the outcome of interest because severe outcomes are less prone to surveillance bias. Because 90% of the injuries occurred in the elderly population are mild conditions and associated with to later-onset of recurrent injuries (51), whether similar increased risk for injuries requiring only outpatient and primary care during the diagnostic process of cancer warrants further evaluation. By including all levels of healthcare visits, such as through using SHR in Study III, we might be able to study the full process of healthcare visit during cancer diagnostic workup, for example, the transfers between healthcare systems involving different healthcare professionals (150). Future studies with more detailed clinical information on the reason of cancer diagnostic workup, the course of an evaluation process, and the decision and action of treatment strategies including also non-surgical treatment are needed.

We found an increased risk of stress-related health outcomes when women were evaluated for a potential breast cancer. Whether or not similar results are seen for other cancer types remains largely unknown. Given the lower survival rate and the worse prognosis in other cancers compared to breast cancer, the health impact of psychological stress in relation to the diagnostic workup of other cancer types is likely to be more influential, for instance, for patients evaluated for a cancer with signs and symptoms that heavily affect quality of life. Studies are therefore needed to investigate the impact of cancer diagnostic workup among these patients.

In this thesis, we found rate increase of different stress-related health outcomes when patients are evaluated for cancer. However, we could not disentangle the impact of psychological stress from the influence of cancer symptoms and pathophysiology. For example, cancer-related pain and tumor-induced inflammation may also contribute to the occurrence of a variety of health outcomes, when acting jointly with stress-induced inflammation. The underlying mechanisms are complex and the contribution of each part requires further investigation. It is possible that stress response may contribute to the initiation and progression of other diseases. We studied some selected health outcomes that are known to be stress-related, other health outcomes such as infection, autoimmune and metabolic diseases, could also be targeted in future research. Furthermore, given the highly stressful experience during cancer evaluation, it is plausible that the psychological burden induced by diagnostic workup may have an adverse impact on cancer survival in general and on patients' quality of life specifically. So far, very little has been done in connecting the experience during cancer diagnostic workup to the long-term health outcomes. It can be speculated that patients who suffer from the diagnostic workup and therapeutic procedures may also be the individuals requiring more healthcare resources, sick leave days, and health reimbursement.

We found that use of anti-inflammatory drugs was associated with a lower risk of unnatural deaths after a cancer diagnosis, reassuring the role of inflammation between stress and its related health outcomes. More studies are warranted to assess whether such medication use could also attenuate other non-fatal stress-related health outcomes. Meanwhile, future research is needed to identify other potential interventions, such as family and social support, in reducing health risks. A better understanding of the inflammatory pathway between stress and stress-

related health outcomes may provide critical insights into mechanisms underlying a variety of stress-related health outcomes in cancer patients. It is of great value to figure out why vulnerability and stress resilience may differ between individuals, from both genetic and non-genetic point of view. Last but not least, taking care of family members with severe diseases can also introduce a high level of psychological burden. Heath adversities in primary caregivers, such as parents, spouse and children of the patient, deserve additional attention both in research and clinically.

10 ACKNOWLEDGEMENTS

This work could not possibly be done without the financial support from the Swedish Cancer Society, the Swedish Research Council for Health, Working Life and Welfare, Swedish Society for Medical Research, China Scholarship Council, and from Karolinska Institutet. The availability of Swedish registers made all the research involved in this thesis possible to conduct. Special thanks to all the people and efforts behind this.

I would like to express my sincere appreciation to my main supervisor **Fang Fang**, who introduced me to MEB family to start this wonderful journey. Thank you for sharing with me your time and profound knowledge in this field, and guiding me to go through all the challenges. Thank you for always keeping the door open for me, whenever I came up to you, work-related or life issues. Your expertise, passion and warm-hearted personality lighten up my way of becoming an independent researcher. Thank you for you trust and encouragement all the way along. I enjoyed the whole advanture!

Maria E C Schelin, my co-supervisor. I was extremely exited about being your student and learning from your experiences on breast cancer field as well as life in MEB back in time. Thank you for hosting me in Skåne and introducing me to SHR. I am grateful for all your advice, understanding and support, to my study and life.

Yang Cao, my co-supervisor, thank you for taking me as your first student in Sweden. You trained me in writing up the first paper and got it published. It is your broad knowledge and attitude towards science that encourages me to search for what I want to do, which leads me to where I am now. Thank you for bearing with me when throwing statistical questions to you at any time and even calling you in evening!

Pär Sparén, my co-supervisor. Thank you for offering NKCx to me and teaching me all the knowledge about cervical cancer screening. Your comments and suggestions were very inspiring and got to the point. I am so impressed by your wisdom, technical mind and optimistic attitude every time I talked to you. Lucky to have you in my supervisor team!

My dearest co-authors and friends, **Unnur Valdimarsdóttir** and **Katja Fall**. You two are so caring, easy to work with, and incredibly knowledgeable! Your smiles in particular inspire me to break my limits. You two made my PhD journey so much rewarding and fulfilling! I have to mention you here, **Donghao Lu**, the real "Doraemon" in life and problem solver! So lucky to work with you! You provide me with countless help from the first day of my study, and through all these years. I enjoyed so much discussing with you in office and over lunch!

Special thanks to all the help and input from my fascinating co-authors: **Anna Jöud**, **Hans-Olov Adami**, **Sven Cnattingius**, **Bengt Andrae**, **Arvid Sjölander**, **Kamila Czene**, **Erica Sloan**, **Adam Walker**, **Karin Smedby**. Thank you for all the thoughtful comments. I learnt so much from you! *Bengt*, thank you for the clinical knowledge and all the help you provide to me. *Arvid*, you are the statistical rock and the best teacher! Thank you for the insightful discussion and to be the chair of my defence.

My sincere gratitude goes to my mentor and first friends in Sweden, Professor **Stephan Rössner** and **Britta Hylander Rössner**. I would never forget the time you both welcomed me to this country, shared with me culture and social norm, and invited me to your sweetest home and summer house! I would not be more grateful to all the fantastic meals you prepared for me and my family. Special thanks to Docent **Xiao-Jun Xu** and **Jing-Xia Hao** who always treat me so nice and host my family every time they were here. Thank you for taking care of so many students and making Stockholm such a delightful place to study and live!

A big thanks to previous as well as current colleagues and friends from our group - Unit of Integrative Epidemiology: **Deniela Mariosa**, **Ruoqing Chen**, **Elisa Longinetti**, **Jianwei Zhu**, **Solmaz Yazdani, Yiqiang Zhan**, **Qianwei Liu**, **Jiangwei Sun**, **Can Cui**, **Kejia Hu**, **Shifeng Lian**, **Weiyao Yin**, **Christina Seiz**, **John Andersson, Amanda Regodón Wallin, Jet Termorshuizen, Anabel Saez Mas, Ulf Kläppe**, **Piero Lamendola**, **Jurate Aleknaviciute, Yuanjun Ma**, **Mizuki Sata**, **Xu Wen**. Thank you for all the fruitful discussions, delightful journal clubs, group meetings as well as wonderful retreats that we all spent together! *Ruoqing*, thank you for acting as a "Fadder", guiding me to get all I need in the first day in MEB. *Jianwei*, thank you for sharing with me your clinical knowledge and all the fantastic food you made for us. *Yuanjun*, thank you for being a good friend and numerous interesting discussions. *Weiyao*, thank you for sharing my anxiousness in the last few months. *Mizuki*, miss the sushi lunch with you and thank you for all the help when we were in conference in Japan. To *Jurate*, for your friendship and all the caring through Wechat! Special thanks to **Ayako Hiyoshi, Ruzan Udumyan** and *Kejia*, for the fantastic advanture we had in Iceland!

My greatest appreciation goes to all **MEBers**! The excellent administrators and IT group who made MEB a lovely environment to work, in particular **Camilla Ahlqvist**, **Alessandra Nanni**, **Gunilla Nilsson Roos**, **Gunilla Sonnebring, Erika Nordenhagen, Frank Pettersson** and **Vivekananda Lanka**. A big thank you to our excellent **PhD student group** that organized great seminars, meetings and student activities. To my previous and current officemates and friends: **Shuyang Yao**, **Donal Barrett**, **Zheng Ning**, **Chen Wang**, **Xinhe Mao** and **Yun Du**. Thank you all for your hot discussion, helpful support and for sharing ups and downs. To my first-to-go team: **Jiayao Lei&Karl Dahlgren, Wei He, Xu Chen, Mei Wang, Haomin Yang, Tingting Huang and Jingru Yu**. Words can not express how grateful I am to know you! You are the best! To all the past and current friends and colleagues that helped me and supported me in different aspects, including but not limited to: **Pouran Almstedt, Jonas Ludviggson, Yudi Pawitan, Marie Reilly, Mark Clements, Sara Bergen, Weimin Ye, Huan Song, Chen Suo, Qi Wang, Amelie Plymoth, Ulrika Zagai, Jiaqi Huang, Zhiwei Liu, Tracy Peters, Alessandra Grotta, Nelson Ndegwa Gichora, Lijie Ding, Tong Gong, Jiangrong Wang, Bojing Liu, Zheng Chang&Ci Song, Le Zhang, Carolyn Cesta, Hannah Bower, Emilio Ugalde Morales, Awad Smew, Andreas Jangmo, Shihua Sun, Laura Ghirardi, Puisan Tan, Qi Chen, Shadi Azam, Philippe Weitz, Xiaoying Kang, Lin Li, Hong Xu, Qian Yang, Yuchen Li** and **Weiwei Bian**. To *Huan*, thank you for sharing your knowledge and experiences to me, by my side and from far away. To *Zheng&Ci*, your friendship and caring lighten up my

way ahead! Thank you to others not included, for your valuable efforts that make MEB a place of scientific magics!

I would like to thank all the previous friends and colleagues from the Unit of Biostatistics in IMM, especially: **Matteo Bottai**, **Paolo Frumento**, **Michele Santacatterina**, **Xin Fang**, **Celia García-Pareja**. I was very impressed by all your passionate discussions in the office, and all the fancy equations on the wall/door. Special thanks to *Xin* and *Celia* for all the girls' talk outside office!

To my sports and entertainment team inside and outside campus: **Erwei Zeng&Hengsha Li, Jie Song&Yanpeng Yang, Ying Shang&Bowen Xia, Meng Xie, Ruyue Zhang&Jiatong Li, Hongying Du&Chencheng Zhang, Xiaolin Zhao&Yufei Zhu, Yiqiao Wang&Yan Xu, Yilin Liu, Zhe Xia, Rui Wang&Yu Qian, Jia Guo, Xicong Liu, Tianle Gao, Zi Ning, Huaqian Zhu** and **Yan Chen&Yu Wang.** My life is so colourful because of you! Thank you all for the treasure time that we spent together!

To my dearest family, it is impossible for me to become who I am without your love and support. 感谢爸爸妈妈们无私的爱与包容，让我成为一个最好的自己！我爱你们！感谢所有亲朋好友的支持与鼓励！To my husband **Tiansheng** and my beloved son **Qingyuan**, love you forever!

11 REFERENCES

1. Baade PD, Fritschi L, Eakin EG. Non-Cancer Mortality among People Diagnosed with Cancer (Australia). Cancer Causes & Control. 2006 Apr;17(3):287–97.

2. Chrousos GP. Stress and disorders of the stress system. Nature Reviews Endocrinology. 2009 Jul;5(7):374–81.

3. Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol. 2017 Apr 1;3(4):524–48.

4. Figueroa-Fankhanel F. Measurement of Stress. Psychiatric Clinics. 2014 Dec 1;37(4):455–87.

5. Saadatmand S, Bretveld R, Siesling S, Tilanus-Linthorst MMA. Influence of tumour stage at breast cancer detection on survival in modern times: population based study in 173 797 patients. BMJ [Internet]. 2015 Oct 6 [cited 2020 Feb 22];351. Available from: https://www.bmj.com/content/351/bmj.h4901

6. Grotenhuis BA, van Hagen P, Wijnhoven BPL, Spaander MCW, Tilanus HW, van Lanschot JJB. Delay in Diagnostic Workup and Treatment of Esophageal Cancer. Journal of Gastrointestinal Surgery. 2010 Mar;14(3):476–83.

7. Richards MA, Westcombe AM, Love SB, Littlejohns P, Ramirez AJ. Influence of delay on survival in patients with breast cancer: a systematic review. Lancet. 1999 Apr 3;353(9159):1119–26.

8. Tørring ML, Murchie P, Hamilton W, Vedsted P, Esteva M, Lautrup M, et al. Evidence of advanced stage colorectal cancer with longer diagnostic intervals: a pooled analysis of seven primary care cohorts comprising 11 720 patients in five countries. Br J Cancer. 2017 Sep 5;117(6):888–97.

9. Ramos M, Esteva M, Cabeza E, Llobera J, Ruiz A. Lack of association between diagnostic and therapeutic delay and stage of colorectal cancer. Eur J Cancer. 2008 Mar;44(4):510–21.

10. Ramos M, Esteva M, Cabeza E, Campillo C, Llobera J, Aguiló A. Relationship of diagnostic and therapeutic delay with survival in colorectal cancer: a review. Eur J Cancer. 2007 Nov;43(17):2467–78.

11. Neal RD, Tharmanathan P, France B, Din NU, Cotton S, Fallon-Ferguson J, et al. Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review. British Journal of Cancer. 2015 Mar 3;112(s1):bjc201548.

12. Probst HB, Hussain ZB, Andersen O. Cancer patient pathways in Denmark as a joint effort between bureaucrats, health professionals and politicians--a national Danish project. Health Policy. 2012 Apr;105(1):65–70.

13. National Institute for Health and Care Excellence: Clinical Guidelines. National Institute for Health and Care Excellence (UK); 2003.

14. Scottish referral guidelines for suspected cancer [Internet]. [cited 2017 Nov 24]. Available from: http://www.healthcareimprovementscotland.org/our_work/cancer_care_improvement/programme_resources/scottish_referral_guidelines.aspx

15. Guideline Development Process - Guidelines Wiki Home - ASCO Guidelines Wiki [Internet]. [cited 2017 Nov 15]. Available from: https://pilotguidelines.atlassian.net/wiki/spaces/GW/pages/8487049/Guideline+Development+Process#GuidelineDevelopmentProcess-Background

16. Jensen H, Tørring ML, Vedsted P. Prognostic consequences of implementing cancer patient pathways in Denmark: a comparative cohort study of symptomatic cancer patients in primary care. BMC Cancer [Internet]. 2017 Sep 6 [cited 2017 Nov 17];17. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5585953/

17. En nationell cancerstrategi för framtiden [Internet]. Stockholm; 2009. Report No.: SOU 2009:11. Available from: http://www.epaac.eu/from_heidi_wiki/Sweden_National_Cancer_Strategy_Swedish.pdf

18. väntetider i cancervården – från remiss till diagnos och behandling [Internet]. [cited 2017 Nov 16]. Available from: http://www.socialstyrelsen.se/publikationer2012/2012-10-28

19. väntetider i cancervården.pdf [Internet]. www.socialstyrelsen.se; Report No.: 2015-12–2. Available from: http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/19942/2015-12-2.pdf

20. Regeringskansliet R och. Measures for shorter waiting times in cancer care [Internet]. Regeringskansliet. 2016 [cited 2017 Nov 17]. Available from: http://www.government.se/articles/2016/01/measures-for-shorter-waiting-times-in-cancer-care/

21. Awsare NS, Green JSA, Aldwinckle B, Hanbury DC, Boustead GB, McNicholas TA. The measurement of psychological distress in men being investigated for the presence of prostate cancer. Prostate cancer and prostatic diseases. 2008;11(4):384–389.

22. Fang F, Fall K, Mittleman MA, Sparén P, Ye W, Adami H-O, et al. Suicide and Cardiovascular Death after a Cancer Diagnosis. New England Journal of Medicine. 2012 Apr 5;366(14):1310–8.

23. Merrill RM, Brown RJ, Alder S, Baker RK, Byrd AD, White GL, et al. Psychological disorders among children and the parents of children undergoing cancer workup. J Psychosoc Oncol. 2007;25(3):1–18.

24. Dworkin MJ, Pittam M. Accuracy of general practitioner referrals to a breast clinic. Ann R Coll Surg Engl. 1996 Nov;78(6):559.

25. Barry MJ. Prostate-Specific–Antigen Testing for Early Diagnosis of Prostate Cancer. New England Journal of Medicine. 2001 May 3;344(18):1373–7.

26. Walter FM, Morris HC, Humphrys E, Hall PN, Prevost AT, Burrows N, et al. Effect of adding a diagnostic aid to best practice to manage suspicious pigmented lesions in primary care: randomised controlled trial. BMJ. 2012 Jul 4;345:e4110.

27. Van Rijsingen MCJ, Hanssen SCA, Groenewoud JMM, Van Der Wilt GJ, Gerritsen M-JP. Referrals by General Practitioners for Suspicious Skin Lesions: The Urgency of Training. Acta Dermato-Venereologica. 2014 Mar 1;94(2):138–41.

28. Gøtzsche PC, Jørgensen KJ. Screening for breast cancer with mammography. Cochrane Database Syst Rev. 2013 Jun 4;(6):CD001877.

29. Loeb S, Bjurlin MA, Nicholson J, Tammela TL, Penson DF, Carter HB, et al. Overdiagnosis and overtreatment of prostate cancer. Eur Urol. 2014 Jun;65(6):1046–55.

30. Brasso K, Ladelund S, Frederiksen BL, Jørgensen T. Psychological distress following fecal occult blood test in colorectal cancer screening--a population-based study. Scand J Gastroenterol. 2010 Oct;45(10):1211–6.

31. Bellardita L, Valdagni R, van den Bergh R, Randsdorp H, Repetto C, Venderbos LDF, et al. How does active surveillance for prostate cancer affect quality of life? A systematic review. Eur Urol. 2015 Apr;67(4):637–45.

32. Brett J, Bankhead C, Henderson B, Watson E, Austoker J. The psychological impact of mammographic screening. A systematic review. Psychooncology. 2005 Nov;14(11):917–38.

33. Lu D, Andersson TML, Fall K, Hultman CM, Czene K, Valdimarsdóttir U, et al. Clinical Diagnosis of Mental Disorders Immediately Before and After Cancer Diagnosis: A Nationwide Matched Cohort Study in Sweden. JAMA Oncol. 2016 Sep 1;2(9):1188–96.

34. Rozanski A, Blumenthal JA, Kaplan J. Impact of Psychological Factors on the Pathogenesis of Cardiovascular Disease and Implications for Therapy. Circulation. 1999 Apr 27;99(16):2192–217.

35. Gernaat S a. M, Ho PJ, Rijnberg N, Emaus MJ, Baak LM, Hartman M, et al. Risk of death from cardiovascular disease following breast cancer: a systematic review. Breast Cancer Res Treat. 2017 Aug;164(3):537–55.

36. Gullette EC, Blumenthal JA, Babyak M, Jiang W, Waugh RA, Frid DJ, et al. Effects of mental stress on myocardial ischemia during daily life. JAMA. 1997 May 21;277(19):1521–6.

37. Jiang W, Babyak M, Krantz DS, Waugh RA, Coleman RE, Hanson MM, et al. Mental stress--induced myocardial ischemia and cardiac events. JAMA. 1996 Jun 5;275(21):1651–6.

38. Hampton T. Cancer Therapy Can Be Hard on the Heart. JAMA. 2010 Mar 17;303(11):1019–20.

39. Coebergh JWW, Janssen-Heijnen MLG, Razenberg PPA. Prevalence of co-morbidity in newly diagnosed patients with cancer: a population-based study. Critical Reviews in Oncology/Hematology. 1998 Feb 1;27(2):97–100.

40. Fall K, Fang F, Mucci LA, Ye W, Andrén O, Johansson J-E, et al. Immediate Risk for Cardiovascular Events and Suicide Following a Prostate Cancer Diagnosis: Prospective Cohort Study. PLOS Medicine. 2009 Dec 15;6(12):e1000197.

41. Fang F, Keating NL, Mucci LA, Adami H-O, Stampfer MJ, Valdimarsdóttir U, et al. Immediate risk of suicide and cardiovascular death after a prostate cancer diagnosis: cohort study in the United States. J Natl Cancer Inst. 2010 Mar 3;102(5):307–14.

42. Cronin-Fenton DP, Søndergaard F, Pedersen LA, Fryzek JP, Cetin K, Acquavella J, et al. Hospitalisation for venous thromboembolism in cancer patients and the general population: a population-based cohort study in Denmark, 1997-2006. Br J Cancer. 2010 Sep 28;103(7):947–53.

43. Anguiano L, Mayer DK, Piven ML, Rosenstein D. A Literature Review of Suicide in Cancer Patients: Cancer Nursing. 2012;35(4):E14–26.

44. Choi Y-N, Kim Y-A, Yun YH, Kim S, Bae J-M, Kim Y-W, et al. Suicide ideation in stomach cancer survivors and possible risk factors. Support Care Cancer. 2014 Feb;22(2):331–7.

45. Misono S, Weiss NS, Fann JR, Redman M, Yueh B. Incidence of suicide in persons with cancer. J Clin Oncol. 2008 Oct 10;26(29):4731–8.

46. Urban D, Rao A, Bressel M, Neiger D, Solomon B, Mileshkin L. Suicide in lung cancer: who is at risk? Chest. 2013 Oct;144(4):1245–52.

47. Yamauchi T, Inagaki M, Yonemoto N, Iwasaki M, Inoue M, Akechi T, et al. Death by suicide and other externally caused injuries following a cancer diagnosis: the Japan Public Health Center-based Prospective Study. Psychooncology. 2014 Sep;23(9):1034–41.

48. Ahn MH, Park S, Lee HB, Ramsey CM, Na R, Kim SO, et al. Suicide in cancer patients within the first year of diagnosis. Psycho-Oncol. 2015 May;24(5):601–7.

49. Lu D, Fall K, Sparén P, Ye W, Adami H-O, Valdimarsdóttir U, et al. Suicide and suicide attempt after a cancer diagnosis among young individuals. Ann Oncol. 2013 Dec;24(12):3112–7.

50. Passik SD, Breitbart WS. Depression in patients with pancreatic carcinoma. Diagnostic and treatment issues. Cancer. 1996 Aug 1;78(3 Suppl):615–26.

51. Ganz DA, Bao Y, Shekelle PG, Rubenstein LZ. Will My Patient Fall? JAMA. 2007 Jan 3;297(1):77–86.

52. Kelsey JL, Procter-Gray E, Hannan MT, Li W. Heterogeneity of Falls Among Older Adults: Implications for Public Health Prevention. Am J Public Health. 2012 Nov;102(11):2149–56.

53. Camidge DR, Stockton DL, Frame S, Wood R, Bain M, Bateman DN. Hospital admissions and deaths relating to deliberate self-harm and accidents within 5 years of a cancer diagnosis: a national study in Scotland, UK. Br J Cancer. 2007 Mar 12;96(5):752–7.

54. Dalela D, Krishna N, Okwara J, Preston MA, Abdollah F, Choueiri TK, et al. Suicide and accidental deaths among patients with non-metastatic prostate cancer. BJU Int. 2016 Aug;118(2):286–97.

55. Bergen H, Hawton K, Kapur N, Cooper J, Steeg S, Ness J, et al. Shared characteristics of suicides and other unnatural deaths following non-fatal self-harm? A multicentre study of risk factors. Psychol Med. 2012 Apr;42(4):727–41.

56. Ganz DA, Latham NK. Prevention of Falls in Community-Dwelling Older Adults. New England Journal of Medicine. 2020 Feb 20;382(8):734–43.

57. Makary MA, Daniel M. Medical error—the third leading cause of death in the US. BMJ. 2016 May 3;i2139.

58. Weingart, S. N., Wilson, R. M., Gibberd, R. W., Harrison, B. Epidemiology of medical error. BMJ. 2000 Mar 18;320(7237):774–7.

59. Brennan TA, Leape LL, Laird NM, Hebert L, Localio AR, Lawthers AG, et al. Incidence of adverse events and negligence in hospitalized patients: results of the Harvard Medical Practice Study I. New England journal of medicine. 1991;324(6):370–376.

60. Wilson RM, Runciman WB, Gibberd RW, Harrison BT, Newby L, Hamilton JD. The Quality in Australian Health Care Study. Med J Aust. 1995 Nov 6;163(9):458–71.

61. Wilson RM, Harrison BT, Gibberd RW, Hamilton JD. An analysis of the causes of adverse events from the Quality in Australian Health Care Study. Med J Aust. 1999 May 3;170(9):411–5.

62. Kable AK, Gibberd RW, Spigelman AD. Adverse events in surgical patients in Australia. Int J Qual Health Care. 2002 Aug;14(4):269–76.

63. Baker GR, Norton PG, Flintoft V, Blais R, Brown A, Cox J, et al. The Canadian Adverse Events Study: the incidence of adverse events among hospital patients in Canada. Can Med Assoc J. 2004 May 25;170(11):1678–86.

64. Leape LL, Lawthers AG, Brennan TA, Johnson WG. Preventing medical injury. QRB Qual Rev Bull. 1993 May;19(5):144–9.

65. Zwaan L, Bruijne M de, Wagner C, Thijs A, Smits M, Wal G van der, et al. Patient Record Review of the Incidence, Consequences, and Causes of Diagnostic Adverse Events. Arch Intern Med. 2010 Jun 28;170(12):1015–21.

66. Arbyn M, Weiderpass E, Bruni L, de Sanjosé S, Saraiya M, Ferlay J, et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. The Lancet Global Health. 2020 Feb;8(2):e191–203.

67. Statistics on cancer [Internet]. Socialstyrelsen. [cited 2017 Nov 28]. Available from: http://www.socialstyrelsen.se/statistik/statistikefteramne/cancer

68. Currin LG, Jack RH, Linklater KM, Mak V, Møller H, Davies EA. Inequalities in the incidence of cervical cancer in South East England 2001–2005: an investigation of population risk factors. BMC Public Health. 2009 Feb 20;9(1):62.

69. Bruni L, Diaz M, Castellsagué M, Ferrer E, Bosch FX, de Sanjosé S. Cervical Human Papillomavirus Prevalence in 5 Continents: Meta-Analysis of 1 Million Women with Normal Cytological Findings. J Infect Dis. 2010 Dec 15;202(12):1789–99.

70. Schiffman M, Herrero R, DeSalle R, Hildesheim A, Wacholder S, Cecilia Rodriguez A, et al. The carcinogenicity of human papillomavirus types reflects viral evolution. Virology. 2005 Jun 20;337(1):76–84.

71. Slattery ML, Robison LM, Schuman KL, French TK, Abbott TM, Overall JC, et al. Cigarette Smoking and Exposure to Passive Smoke Are Risk Factors for Cervical Cancer. JAMA. 1989 Mar 17;261(11):1593–8.

72. International Collaboration of Epidemiological Studies of Cervical Cancer, Appleby P, Beral V, Berrington de González A, Colin D, Franceschi S, et al. Cervical cancer and hormonal contraceptives: collaborative reanalysis of individual data for 16,573 women with cervical cancer and 35,509 women without cervical cancer from 24 epidemiological studies. Lancet. 2007 Nov 10;370(9599):1609–21.

73. Liu Z-C, Liu W-D, Liu Y-H, Ye X-H, Chen S-D. Multiple Sexual Partners as a Potential Independent Risk Factor for Cervical Cancer: a Meta-analysis of Epidemiological Studies. Asian Pac J Cancer Prev. 2015;16(9):3893–900.

74. Ostör AG. Natural history of cervical intraepithelial neoplasia: a critical review. Int J Gynecol Pathol. 1993 Apr;12(2):186–92.

75. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. The Lancet. 2007 Sep 8;370(9590):890–907.

76. Andrae B, Andersson TM-L, Lambert PC, Kemetli L, Silfverdal L, Strander B, et al. Screening and cervical cancer cure: population based cohort study. BMJ. 2012 Mar 1;344:e900.

77. Kleppe SN. Nationellt Kvalitetsregister för Cervixcancerprevention (NKCx). :87.

78. Kavanagh AM, Broom DH. Women's understanding of abnormal cervical smear test results: a qualitative interview study. BMJ. 1997 May 10;314(7091):1388.

79. McCaffery K, Waller J, Nazroo J, Wardle J. Social and psychological impact of HPV testing in cervical screening: a qualitative study. Sex Transm Infect. 2006 Apr;82(2):169–74.

80. O'Connor M, Gallagher P, Waller J, Martin CM, O'Leary JJ, Sharp L, et al. Adverse psychological outcomes following colposcopy and related procedures: a systematic review. BJOG. 2016 Jan;123(1):24–38.

81. Bell S, Porter M, Kitchener H, Fraser C, Fisher P, Mann E. Psychological Response to Cervical Screening. Preventive Medicine. 1995 Nov 1;24(6):610–6.

82. Rogstad KE. The psychological impact of abnormal cytology and colposcopy. BJOG. 2002 Apr;109(4):364–8.

83. Sharp L, Cotton S, Carsin A-E, Gray N, Thornton A, Cruickshank M, et al. Factors associated with psychological distress following colposcopy among women with low-grade abnormal cervical cytology: a prospective study within the Trial Of Management of Borderline and Other Low-grade Abnormal smears (TOMBOLA). Psychooncology. 2013 Feb;22(2):368–80.

84. Hoffmann TC, Del Mar C. Patients' expectations of the benefits and harms of treatments, screening, and tests: a systematic review. JAMA Intern Med. 2015 Feb;175(2):274–86.

85. Hoffmann TC, Del Mar C. Clinicians' Expectations of the Benefits and Harms of Treatments, Screening, and Tests: A Systematic Review. JAMA Intern Med. 2017 Mar 1;177(3):407–19.

86. Habbema D, Weinmann S, Arbyn M, Kamineni A, Williams AE, M.C.M. de Kok I, et al. Harms of cervical cancer screening in the United States and the Netherlands. Int J Cancer. 2017 Mar 1;140(5):1215–22.

87. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.

88. Fitzmaurice C, Abate D, Abbasi N, Abbastabar H, Abd-Allah F, Abdel-Rahman O, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2017: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol. 2019 Dec 1;5(12):1749–68.

89. Harbeck N, Gnant M. Breast cancer. The Lancet. 2017 Mar 18;389(10074):1134–50.

90. American Cancer Society. Cancer Treatment and Survivorship Facts and Figures 2016-2017 [Internet]. Atlanta, American Cancer Society; 2016. Available from: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/cancer-treatment-and-survivorship-facts-and-figures/cancer-treatment-and-survivorship-facts-and-figures-2016-2017.pdf

91. Berrino F, De Angelis R, Sant M, Rosso S, Lasota MB, Coebergh JW, et al. Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995–99: results of the EUROCARE-4 study. The Lancet Oncology. 2007 Sep 1;8(9):773–83.

92. Berry DA, Cronin KA, Plevritis SK, Fryback DG, Clarke L, Zelen M, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. New England Journal of Medicine. 2005;353(17):1784–1792.

93. McCormack VA, Silva I dos S. Breast Density and Parenchymal Patterns as Markers of Breast Cancer Risk: A Meta-analysis. Cancer Epidemiol Biomarkers Prev. 2006 Jun 1;15(6):1159–69.

94. McPherson K, Steel CM, Dixon JM. Breast cancer—epidemiology, risk factors, and genetics. BMJ. 2000 Sep 9;321(7261):624–8.

95. Collaborative Group on Hormonal Factors in Breast Cancer. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. Lancet. 2001 Oct 27;358(9291):1389–99.

96. Antoniou A, Pharoah PDP, Narod S, Risch HA, Eyfjord JE, Hopper JL, et al. Average Risks of Breast and Ovarian Cancer Associated with BRCA1 or BRCA2 Mutations Detected in Case Series Unselected for Family History: A Combined Analysis of 22 Studies. The American Journal of Human Genetics. 2003 May 1;72(5):1117–30.

97. Lundqvist A, Andersson E, Ahlberg I, Nilbert M, Gerdtham U. Socioeconomic inequalities in breast cancer incidence and mortality in Europe—a systematic review and meta-analysis. Eur J Public Health. 2016 Oct;26(5):804–13.

98. Investigators WG for the WHI. Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results From the Women's Health Initiative Randomized Controlled Trial. JAMA. 2002 Jul 17;288(3):321–33.

99. Wright RM, McManaman JL, Repine JE. Alcohol-induced breast cancer: a proposed mechanism. Free Radic Biol Med. 1999 Feb;26(3–4):348–54.

100. Lorincz AM. Molecular links between obesity and breast cancer. Endocrine Related Cancer. 2006 Jun 1;13(2):279–92.

101. Virnig BA, Tuttle TM, Shamliyan T, Kane RL. Ductal Carcinoma In Situ of the Breast: A Systematic Review of Incidence, Treatment, and Outcomes. J Natl Cancer Inst. 2010 Feb 3;102(3):170–8.

102. Mooney KL, Bassett LW, Apple SK. Upgrade rates of high-risk breast lesions diagnosed on core needle biopsy: a single-institution experience and literature review. Mod Pathol. 2016 Dec;29(12):1471–84.

103. Tabar L, Yen M-F, Vitak B, Chen H-HT, Smith RA, Duffy SW. Mammography service screening and mortality in breast cancer patients: 20-year follow-up before and after introduction of screening. Lancet. 2003 Apr 26;361(9367):1405–10.

104. Myers ER, Moorman P, Gierisch JM, Havrilesky LJ, Grimm LJ, Ghate S, et al. Benefits and Harms of Breast Cancer Screening: A Systematic Review. JAMA. 2015 Oct 20;314(15):1615–34.

105. Autier P, Koechlin A, Smans M, Vatten L, Boniol M. Mammography screening and breast cancer mortality in Sweden. J Natl Cancer Inst. 2012 Jul 18;104(14):1080–93.

106. Screening för bröstcancer-Rekommendation och bedömningsunderlag [Internet]. Available from: http://www.socialstyrelsen.se/SiteCollectionDocuments/screening-brostcancer-rekommendation.pdf

107. Mehnert A, Brähler E, Faller H, Härter M, Keller M, Schulz H, et al. Four-week prevalence of mental disorders in patients with cancer across major tumor entities. J Clin Oncol. 2014 Nov 1;32(31):3540–6.

108. Ellman R, Angeli N, Christians A, Moss S, Chamberlain J, Maguire P. Psychiatric morbidity associated with screening for breast cancer. Br J Cancer. 1989 Nov;60(5):781–4.

109. Yang H, Brand JS, Fang F, Chiesa F, Johansson ALV, Hall P, et al. Time-dependent risk of depression, anxiety, and stress-related disorders in patients with invasive and in situ breast cancer. Int J Cancer. 2017 Feb 15;140(4):841–52.

110. Bond M, Pavey T, Welch K, Cooper C, Garside R, Dean S, et al. Systematic review of the psychological consequences of false-positive screening mammograms. Health Technol Assess [Internet]. 2013 Mar [cited 2017 Nov 29];17(13). Available from: https://www.journalslibrary.nihr.ac.uk/hta/hta17130/

111. Scaf-Klomp W, Sanderman R, van de Wiel HB, Otter R, van den Heuvel WJ. Distressed or relieved? Psychological side effects of breast cancer screening in The Netherlands. J Epidemiol Community Health. 1997 Dec;51(6):705–10.

112. von Bülow B. [Psychological consequences of breast cancer screening among healthy women]. Ugeskr Laeg. 2000 Feb 21;162(8):1053–9.

113. Schairer C, Brown LM, Chen BE, Howard R, Lynch CF, Hall P, et al. Suicide after breast cancer: an international population-based study of 723,810 women. J Natl Cancer Inst. 2006 Oct 4;98(19):1416–9.

114. Riihimäki M, Thomsen H, Brandt A, Sundquist J, Hemminki K. Death causes in breast cancer patients. Ann Oncol. 2012 Mar 1;23(3):604–10.

115. Cohen S, Janicki-Deverts D, Miller GE. Psychological Stress and Disease. JAMA. 2007 Oct 10;298(14):1685–7.

116. Walker AJ, Card TR, West J, Crooks C, Grainge MJ. Incidence of venous thromboembolism in patients with cancer – A cohort study using linked United Kingdom databases. European Journal of Cancer. 2013 Apr 1;49(6):1404–13.

117. Bruening W. Systematic Review: Comparative Effectiveness of Core-Needle and Open Surgical Biopsy to Diagnose Breast Lesions. Annals of Internal Medicine. 2010 Feb 16;152(4):238.

118. Liu Y-Z, Wang Y-X, Jiang C-L. Inflammation: The Common Pathway of Stress-Related Diseases. Front Hum Neurosci [Internet]. 2017 Jun 20 [cited 2019 Aug 23];11. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5476783/

119. Rohleder N. Stimulation of systemic low-grade inflammation by psychosocial stress. Psychosom Med. 2014 Apr;76(3):181–9.

120. Elenkov IJ. Neurohormonal-cytokine interactions: Implications for inflammation, common human diseases and well-being. Neurochemistry International. 2008 Jan 1;52(1):40–51.

121. Maydych V. The Interplay Between Stress, Inflammation, and Emotional Attention: Relevance for Depression. Front Neurosci [Internet]. 2019 Apr 24 [cited 2020 Feb 19];13. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6491771/

122. Benros ME, Waltoft BL, Nordentoft M, Ostergaard SD, Eaton WW, Krogh J, et al. Autoimmune diseases and severe infections as risk factors for mood disorders: a nationwide study. JAMA Psychiatry. 2013 Aug;70(8):812–20.

123. Goeden N, Velasquez J, Arnold KA, Chan Y, Lund BT, Anderson GM, et al. Maternal Inflammation Disrupts Fetal Neurodevelopment via Increased Placental Output of Serotonin to the Fetal Brain. J Neurosci. 2016 01;36(22):6041–9.

124. Meehan C, Harms L, Frost JD, Barreto R, Todd J, Schall U, et al. Effects of immune activation during early or late gestation on schizophrenia-related behaviour in adult rat offspring. Brain Behav Immun. 2017 Jul;63:8–20.

125. Sørensen HJ, Mortensen EL, Reinisch JM, Mednick SA. Association between prenatal exposure to bacterial infection and risk of schizophrenia. Schizophr Bull. 2009 May;35(3):631–7.

126. Khandaker GM, Zimbron J, Lewis G, Jones PB. Prenatal maternal infection, neurodevelopment and adult schizophrenia: a systematic review of population-based studies. Psychol Med. 2013 Feb;43(2):239–57.

127. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med. 2009 Feb;71(2):171–86.

128. Ming Z, Criswell HE, Breese GR. Evidence for TNFα action on excitatory and inhibitory neurotransmission in the central amygdala: a brain site influenced by stress. Brain Behav Immun. 2013 Oct;33:102–11.

129. Vollmer-Conna U, Fazou C, Cameron B, Li H, Brennan C, Luck L, et al. Production of pro-inflammatory cytokines correlates with the symptoms of acute sickness behaviour in humans. Psychol Med. 2004 Oct;34(7):1289–97.

130. Kendal WS, Kendal WM. Comparative risk factors for accidental and suicidal death in cancer patients. Crisis. 2012;33(6):325–34.

131. Felger JC, Treadway MT. Inflammation Effects on Motivation and Motor Activity: Role of Dopamine. Neuropsychopharmacology. 2017 Jan;42(1):216–41.

132. Guo Z, Wills P, Viitanen M, Fastbom J, Winblad B. Cognitive Impairment, Drug Use, and the Risk of Hip Fracture in Persons over 75 Years Old: A Community-based Prospective Study. Am J Epidemiol. 1998 Nov 1;148(9):887–92.

133. Holtzer R, Friedman R, Lipton RB, Katz M, Xue X, Verghese J. The relationship between specific cognitive functions and falls in aging. Neuropsychology. 2007 Sep;21(5):540–8.

134. Köhler O, Benros ME, Nordentoft M, Farkouh ME, Iyengar RL, Mors O, et al. Effect of Anti-inflammatory Treatment on Depression, Depressive Symptoms, and Adverse Effects: A Systematic Review and Meta-analysis of Randomized Clinical Trials. JAMA Psychiatry. 2014 Dec 1;71(12):1381–91.

135. Müller N. COX-2 Inhibitors, Aspirin, and Other Potential Anti-Inflammatory Treatments for Psychiatric Disorders. Front Psychiatry [Internet]. 2019 May 31 [cited 2019 Aug 13];10. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6555131/

136. J R Vane. The Fight Against Rheumatism: From Willow Bark to COX-1 Sparing Drugs. J Physiol Pharmacol. 51(4):573–86.

137. Gallagher PJ, Castro V, Fava M, Weilburg JB, Murphy SN, Gainer VS, et al. Antidepressant response in patients with major depression exposed to NSAIDs: a pharmacovigilance study. Am J Psychiatry. 2012 Oct;169(10):1065–72.

138. Kessing LV, Rytgaard HC, Gerds TA, Berk M, Ekstrøm CT, Andersen PK. New drug candidates for depression - a nationwide population-based study. Acta Psychiatr Scand. 2019 Jan;139(1):68–77.

139. Zhong S, Zhang X, Chen L, Ma T, Tang J, Zhao J. Association between aspirin use and mortality in breast cancer patients: a meta-analysis of observational studies. Breast Cancer Res Treat. 2015 Feb;150(1):199–207.

140. Frisk G, Ekberg S, Lidbrink E, Eloranta S, Sund M, Fredriksson I, et al. No association between low-dose aspirin use and breast cancer outcomes overall: a Swedish population-based study. Breast Cancer Res [Internet]. 2018 [cited 2019 Oct 3];20. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6247765/

141. Barlow L, Westergren K, Holmberg L, Talbäck M. The completeness of the Swedish Cancer Register – a sample survey for year 1998. Acta Oncologica. 2009 Jan 1;48(1):27–33.

142. Brooke HL, Talbäck M, Hörnblad J, Johansson LA, Ludvigsson JF, Druid H, et al. The Swedish cause of death register. Eur J Epidemiol. 2017;32(9):765–73.

143. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim J-L, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011 Jun 9;11:450.

144. Wettermark B, Hammar N, MichaelFored C, Leimanis A, Olausson PO, Bergman U, et al. The new Swedish Prescribed Drug Register—Opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiology and Drug Safety. 16(7):726–35.

145. World Health Organization (WHO). Guidelines for ATC classification and DDD assignment [Internet]. WHO Collaborating Centre for Drug Statistics; Available from: https://www.whocc.no/

146. Ludvigsson JF, Almqvist C, Bonamy A-KE, Ljung R, Michaëlsson K, Neovius M, et al. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol. 2016 Feb;31(2):125–36.

147. Population and housing census 1960–1990 (TPR) [Internet]. Statistiska Centralbyrån. [cited 2020 Feb 24]. Available from: http://www.scb.se/en/finding-statistics/statistics-by-subject-area/population/population-size-and-changes/population-and-housing-census-1960-1990-tpr/

148. NKCx [Internet]. Swedish National Cervical Screening Registry_Analysis. [cited 2018 May 22]. Available from: http://www.nkcx.se/index_e.htm

149. Quick facts about Skåne - Region Skåne [Internet]. [cited 2018 Mar 22]. Available from: https://www.skane.se/organisation-politik/om-region-skane/Statistik-om-Skane/kort-fakta-skane/

150. Löfvendahl S, Schelin MEC, Jöud A. The value of the Skåne Health-care Register: Prospectively collected individual-level data for population-based studies. Scand J Public Health. 2019 Dec 8;1403494819868042.

151. Ludvigsson JF, Håberg SE, Knudsen GP, Lafolie P, Zoega H, Sarkkola C, et al. Ethical aspects of registry-based research in the Nordic countries. Clin Epidemiol. 2015 Nov 23;7:491–508.

152. Smoking, stress, and negative affect: Correlation, causation, and context across stages of smoking. - PsycNET [Internet]. [cited 2020 Feb 23]. Available from: https://psycnet.apa.org/record/2003-01977-006

153. Herman JP, McKlveen JM, Solomon MB, Carvalho-Netto E, Myers B. Neural regulation of the stress response: glucocorticoid feedback mechanisms. Braz J Med Biol Res. 2012 Apr;45(4):292–8.

154. Injury Data and Resources - ICD Injury Matrices [Internet]. 2019 [cited 2020 Jan 27]. Available from: https://www.cdc.gov/nchs/injury/injury_matrices.htm

155. ICD-10 Version:2010 [Internet]. [cited 2020 Jan 27]. Available from: https://icd.who.int/browse10/2010/en#/XX

156. Armstrong BG, Gasparrini A, Tobias A. Conditional Poisson models: a flexible alternative to conditional logistic case cross-over analysis. BMC Med Res Methodol [Internet]. 2014 Nov 24 [cited 2018 Sep 3];14. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4280686/

157. Dillner J. Cervical cancer screening in Sweden. European Journal of Cancer. 2000;5.

158. Balasubramaniam K, Elnegaard S, Rasmussen S, Haastrup PF, Christensen R dePont, Søndergaard J, et al. Lifestyle, socioeconomic status and healthcare seeking among women with gynaecological cancer alarm symptoms: a combined questionnaire-based and register-based population study. BMJ Open [Internet]. 2018 Jul 1 [cited 2019 Nov 12];8(7). Available from: https://bmjopen.bmj.com/content/8/7/e021815

159. Waiting time SVF breast cancer [Internet]. [cited 2018 Mar 23]. Available from: https://www.cancercentrum.se/samverkan/cancerdiagnoser/brost/vardforlopp-brostcancer/redovisning-vantetid/

160. Mansournia MA, Altman DG. Population attributable fraction. BMJ [Internet]. 2018 Feb 22 [cited 2020 Mar 5];360. Available from: https://www.bmj.com/content/360/bmj.k757

161. Newson RB. Attributable and Unattributable Risks and Fractions and other Scenario Comparisons. The Stata Journal. 2013 Dec 1;13(4):672–98.

162. Phd JW, Msc AP, Mrcgp DS. Psychological consequences of positive results in cervical cancer screening. Psychology & Health. 1995 Apr 1;10(3):185–94.

163. Korfage IJ, Essink-Bot M-L, Westenberg SM, Helmerhorst T, Habbema JDF, van Ballegooijen M. How distressing is referral to colposcopy in cervical cancer screening?: a prospective quality of life study. Gynecol Oncol. 2014 Jan;132(1):142–8.

164. Shen Q, Lu D, Schelin MEC, Jöud A, Cao Y, Adami H-O, et al. Injuries before and after diagnosis of cancer: nationwide register based study. BMJ. 2016 Aug 31;i4218.

165. Mouridsen H, Keshaviah A, Coates AS, Rabaglio M, Castiglione-Gertsch M, Sun Z, et al. Cardiovascular adverse events during adjuvant endocrine therapy for early breast cancer using letrozole or tamoxifen: safety analysis of BIG 1-98 trial. J Clin Oncol. 2007 Dec 20;25(36):5715–22.

166. Hooning MJ, Botma A, Aleman BMP, Baaijens MHA, Bartelink H, Klijn JGM, et al. Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. J Natl Cancer Inst. 2007 Mar 7;99(5):365–75.

167. Réus GZ, Fries GR, Stertz L, Badawy M, Passos IC, Barichello T, et al. The role of inflammation and microglial activation in the pathophysiology of psychiatric disorders. Neuroscience. 2015 Aug 6;300:141–54.

168. Diakos CI, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. Lancet Oncol. 2014 Oct;15(11):e493-503.

169. Arndt V, Stürmer T, Stegmaier C, Ziegler H, Dhom G, Brenner H. Socio-demographic factors, health behavior and late-stage diagnosis of breast cancer in Germany: A population-based study. Journal of Clinical Epidemiology. 2001 Jul 1;54(7):719–27.

170. Nelson HD, Pappas M, Cantor A, Griffin J, Daeges M, Humphrey L. Harms of Breast Cancer Screening: Systematic Review to Update the 2009 U.S. Preventive Services Task Force Recommendation. Ann Intern Med. 2016 Feb 16;164(4):256–67.

171. Brodersen J, Jørgensen KJ, Gøtzsche PC. The benefits and harms of screening for cancer with a focus on breast screening. Pol Arch Med Wewn. 2010 Mar;120(3):89–94.

172. Henson KE, Brock R, Charnock J, Wickramasinghe B, Will O, Pitman A. Risk of Suicide After Cancer Diagnosis in England. JAMA Psychiatry. 2019 Jan 1;76(1):51–60.

173. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009 May 30;373, 373(9678, 9678):1849, 1849–60.

174. Rothwell PM, Fowkes FGR, Belch JFF, Ogawa H, Warlow CP, Meade TW. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet. 2011 Jan 1;377(9759):31–41.

175. Jackson SS, Pfeiffer RM, Liu Z, Anderson LA, Tsai H-T, Gadalla SM, et al. Association Between Aspirin Use and Biliary Tract Cancer Survival. JAMA Oncol [Internet]. 2019 Oct 17 [cited 2019 Nov 15]; Available from: https://jamanetwork.com/journals/jamaoncology/fullarticle/2752784

176. Berk M, Dean O, Drexhage H, McNeil JJ, Moylan S, O'Neil A, et al. Aspirin: a review of its neurobiological properties and therapeutic potential for mental illness. BMC Medicine. 2013 Mar 18;11(1):74.

177. Mortensen P, Agerbo E, Erikson T, Qin P, Westergaard-Nielsen N. Psychiatric illness and risk factors for suicide in Denmark. The Lancet. 2000 Jan 1;355(9197):9–12.

178. Szanto K. Cognitive deficits: Underappreciated contributors to suicide. Am J Geriatr Psychiatry. 2017 Jun;25(6):630–2.

179. Qiu L, Yang Q, Sun N, Li D, Zhao Y, Li X, et al. Association between depression and the risk for fracture: a meta-analysis and systematic review. BMC Psychiatry. 2018 17;18(1):336.

180. Lach HW, Harrison BE, Phongphanngam S. Falls and Fall Prevention in Older Adults With Early-Stage Dementia: An Integrative Review. Res Gerontol Nurs. 2017 01;10(3):139–48.

181. Walker AK, Chang A, Ziegler AI, Dhillon HM, Vardy JL, Sloan EK. Low dose aspirin blocks breast cancer-induced cognitive impairment in mice. PLOS ONE. 2018 Dec 10;13(12):e0208593.

182. Loas G. Anhedonia and suicide: a 6.5-yr. follow-up study of patients hospitalised for a suicide attempt. Psychol Rep. 2007 Feb;100(1):183–90.

183. Conaghan PG. A turbulent decade for NSAIDs: update on current concepts of classification, epidemiology, comparative efficacy, and toxicity. Rheumatol Int. 2012 Jun;32(6):1491–502.

184. García Rodríguez LA, Barreales Tolosa L. Risk of upper gastrointestinal complications among users of traditional NSAIDs and COXIBs in the general population. Gastroenterology. 2007 Feb;132(2):498–506.

185. Antman Elliott M., Bennett Joel S., Daugherty Alan, Furberg Curt, Roberts Harold, Taubert Kathryn A. Use of Nonsteroidal Antiinflammatory Drugs. Circulation. 2007 Mar 27;115(12):1634–42.

186. Recommendations for use of selective and nonselective nonsteroidal antiinflammatory drugs: An American College of Rheumatology white paper. Arthritis Care & Research. 2008;59(8):1058–73.

187. Riihimaki M, Thomsen H, Brandt A, Sundquist J, Hemminki K. What Do Prostate Cancer Patients Die Of? The Oncologist. 2011 Feb 1;16(2):175–81.

188. Riihimäki M, Thomsen H, Sundquist K, Hemminki K. Colorectal cancer patients: what do they die of? Frontline Gastroenterology. 2012 Jul 1;3(3):143–9.

189. Iversen LH, Bülow S, Christensen IJ, Laurberg S, Harling H. Postoperative medical complications are the main cause of early death after emergency surgery for colonic cancer. BJS (British Journal of Surgery). 2008;95(8):1012–9.

190. Hoang-Xuan K, Camilleri-Broët S, Soussain C. Recent advances in primary CNS lymphoma. Current Opinion in Oncology. 2004 Nov;16(6):601–606.

191. Goodwin JS, Hunt WC, Samet JM. Determinants of cancer therapy in elderly patients. Cancer. 1993;72(2):594–601.

192. Andrae B, Kemetli L, Sparén P, Silfverdal L, Strander B, Ryd W, et al. Screening-preventable cervical cancer risks: evidence from a nationwide audit in Sweden. J Natl Cancer Inst. 2008 May 7;100(9):622–9.

193. TOMBOLA (Trial Of Management of Borderline and Other Low-grade Abnormal smears) Group, Sharp L, Cotton S, Cochran C, Gray N, Little J, et al. After-effects reported by women following colposcopy, cervical biopsies and LLETZ: results from the TOMBOLA trial. BJOG. 2009 Oct;116(11):1506–14.

194. Breyer B, Despot A, Predanic M, Judin S. Characteristics of blood flow in cancer of the uterine cervix. Ultrasound Obstet Gynecol. 1993 Jul 1;3(4):268–70.

195. Azerkan F, Sparén P, Sandin S, Tillgren P, Faxelid E, Zendehdel K. Cervical screening participation and risk among Swedish-born and immigrant women in Sweden. Int J Cancer. 2012 Feb 15;130(4):937–47.

196. Bahirwani R, Reddy KR. Drug-induced liver injury due to cancer chemotherapeutic agents. Semin Liver Dis. 2014 May;34(2):162–71.

197. James JT. A new, evidence-based estimate of patient harms associated with hospital care. J Patient Saf. 2013 Sep;9(3):122–8.

198. Frieden TR. Evidence for Health Decision Making — Beyond Randomized, Controlled Trials. New England Journal of Medicine. 2017 Aug 3;377(5):465–75.

199. Murad MH, Asi N, Alsawas M, Alahdab F. New evidence pyramid. Evidence Based Medicine. 2016 Aug;21(4):125–7.

200. Whitaker HJ, Hocine MN, Farrington CP. The methodology of self-controlled case series studies. Stat Methods Med Res. 2009 Feb 1;18(1):7–26.

201. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of Myocardial Infarction and Stroke after Acute Infection or Vaccination. New England Journal of Medicine. 2004 Dec 16;351(25):2611–8.

202. Farrington CP, Whitaker HJ. Semiparametric analysis of case series data. Journal of the Royal Statistical Society: Series C (Applied Statistics). 2006;55(5):553–94.

203. Tøllefsen IM, Helweg-Larsen K, Thiblin I, Hem E, Kastrup MC, Nyberg U, et al. Are suicide deaths under-reported? Nationwide re-evaluations of 1800 deaths in Scandinavia. BMJ Open. 2015 Nov;5(11):e009120.